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REFLEX CORONARY ARTERY SPASM FOLLOWING SUDDEN OCCLUSION OF OTHER CORONARY BRANCHES

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The serious effects of coronary artery disease on the heart are due to an inadequate blood supply to the heart muscle. Usually the reduction in the blood supply is associated with a diminution in the caliber of the coronary arteries, either local or general, by atherosclerosis. On the other hand, there are conditions which, even in the presence of normal coronary arteries, may result in a decreased blood supply to the myocardium.[1]

It is possible, also, that myocardial ischemia may result from temporary spasm of coronary arteries. This could take place, as a result of a decrease in or loss of the dilator response of the coronary arteries to physiologic stimuli, whether the arteries were atherosclerotic or normal.

Although it has been impossible so far to reproduce experimentally true human coronary sclerosis, it is possible to simulate the effects of the resulting myocardial ischemia by ligation of one or more branches of a coronary artery in the dog. Many authors have reported on the pathologic changes resulting from acute ligation of coronary arteries in different species of experimental animals. This literature, covering over one hundred years, has already been reviewed.[2]

With the advent of the string galvanometer (1903) accurate electrocardiograms were made possible, and in later years the electrocardiographic changes following experimental coronary artery occlusion were studied by many persons. The results of such experiments have been used widely in the interpretation of clinical findings, particularly after

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1. White, P. D.: Heart Disease, New York, The Macmillan Company, 1934.

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Herrick [3] had shown that coronary thrombosis was a clinical entity which could be recognized during life.

The earlier workers conducted their experiments on anesthetized animals and naturally were unable to demonstrate pain following coronary occlusion. Other workers, including Sutton and Lueth,[4] have described experiments in which occlusion of the coronary arteries in conscious dogs caused pain, nausea and vomiting. It has also been found that temporary occlusion caused pain, apparently the result of a sudden decrease in the blood supply to the heart muscle. Complete occlusion in conscious dogs, however, does not lead to permanent pain.

It is important, at this point, to consider whether temporary ischemia of the myocardium will produce persistent changes in the heart muscle. The work on cats recently reported by Blumgart and his associates [5] showed that when temporary occlusion was maintained for fifteen minutes or more electrocardiographic changes persisted for at least twenty-two days. When the occlusion was maintained for five to ten minutes the electrocardiographic changes lasted for five to ten days. The first electrocardiographic changes characteristic of ischemia occurred within one minute. In dogs they found no gross or microscopic evidence of necrosis following temporary occlusion lasting from five to twenty minutes. When the occlusion was maintained for longer periods definite areas of necrosis were evident.

Thus an explanation is possible for the occurrence of electrocardiographic and, later, histologic changes in the myocardium of patients in the absence of coronary thrombosis.

It is well known that many patients with or without a history of angina pectoris die suddenly of a "heart attack." In many cases no evidence of coronary thrombosis can be obtained at autopsy. There is also a fairly large group of cases in which the severity of the symptoms of "coronary disease" is out of all proportion to the extent of the pathologic changes found in the coronary arteries or to the size of the infarcted area as observed at autopsy.

The purpose of the present paper is to report experiments which indicate that the high mortality following acute occlusion of one branch of a coronary artery in the conscious dog cannot be accounted for by the extent of the experimentally produced infarct. This work suggests

3. Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, J. A. M. A. **59**:2015 (Dec. 7) 1912; Thrombosis of the Coronary Arteries, ibid. **72**:387 (Feb. 8) 1919.

4. Sutton, D. C., and Lueth, H.: Disease of Coronary Arteries, St. Louis, C. V. Mosby Company, 1932.

5. Blumgart, H. L.; Hoff, H.; Landowne, M., and Schlesinger, M. J.: Experimental Studies on the Effect of Temporary Occlusion of Coronary Arteries, Tr. A. Am. Physicians **42**:210, 1937.

that such mortality is the result of the development of a relatively large area of ischemia, brought about by spasm of collateral arterial branches, in addition to the original ischemic area.

EXPERIMENTS

Normal healthy dogs of varying ages were used. Electrocardiograms were taken on at least three successive days before operation and at desired intervals following coronary artery occlusion. In some of the animals readings of the blood pressure were obtained by direct femoral puncture before, during and after the experimental occlusion.

The animals which did not survive the occlusion were examined immediately after death, and the location of the ligature and ischemic areas was verified. The gross findings were recorded on a mimeographed diagram of the dog heart. Histologic sections were taken from various areas of the hearts of all the animals used.

Each surviving animal was kept lying quietly on his side for one to two hours after the ligation. After this period the animal was removed to its cage and no restraint was made on its movements. In view of the already weakened myocardium, any excessive exertion might readily have resulted in cardiac failure or rupture. In spite of this possibility the death of any animal which died within twenty-four hours of ligation was listed as sudden death.

Electrocardiograms and records of the blood pressure were taken for the surviving dogs for as long as nine months after the experimental occlusion.

For operation, ¼ grain (0.16 Gm.) of morphine and ether administered intratracheally were used in all cases. An aseptic technic was employed. After careful dissection a ligature was passed under either the proximal portion of the anterior descending branch or the circumflex branch of the left coronary artery. A special ligature carrier was used for this purpose, so that pulling, rolling or constriction of the artery would be prevented.

Four groups of animals were prepared in this way. In group 1 the anterior descending branch was completely ligated. In group 2 the circumflex branch was ligated. In group 3 a ligature was placed around the anterior descending branch and loosely tied with a single knot. The two ends of the ligature were brought to the surface of the chest at the ends of the incision, the chest was closed and the superficial layers were sutured. A sufficient length of slack ligature was left within the chest so that movement of the heart would not tighten the loose knot. After a sterile dressing was applied to the wound the animal was allowed to recover from the anesthesia. In group 4 a loose ligature was placed around the circumflex branch and the animal treated as in group 3.

On the day following the operation each animal in groups 3 and 4 was placed on its right side. Electrocardiograms were taken and the two ends of the loose ligature pulled tightly. The ends of the ligature protruding through the chest wall were cut, so that the heart would not be pulled permanently out of position. Thus acute occlusion of a branch of a coronary artery in the conscious dog was effected.

GROUP 1.—*Sudden occlusion of the anterior descending branch of the left coronary artery during anesthesia.*

Seventeen dogs, including 7 litter mates 6 months of age, were used in this series. The anterior descending branch was ligated ½ inch (1.27 cm.) from the aorta. Electrocardiograms were taken before, during and at intervals after the ligation.

Only one death occurred in this group. On the basis of this figure one might expect a mortality of less than 10 per cent.

Pathologic Changes.—In order to follow the pathologic changes occurring in the heart, the animals were killed one-half, two and one-half and twelve hours and two, three, seven, fourteen and twenty-one days after the occlusion. Routine sections were taken for microscopic examination from the infarcted and normal areas of each heart.

Gross examination revealed that few changes had taken place in the heart muscle thirty minutes after ligation. Within two and one-half hours, however, the infarcted area became dark and hard and could be differentiated readily from the surrounding myocardium. At seven days the infarcted area appeared dark, soft and very weak (fig. 3 *A*). It is at this period that rupture of the ventricle would most likely occur. Considerable fibrosis was evident at fourteen days, and by twenty-four days the infarcted area was noticeable only as a dense, whitish contracted scar.

The progressive microscopic changes which take place in the myocardium after occlusion are illustrated in figures 1, 2 and 3.

Within thirty minutes after occlusion variations in the staining quality of the muscle were noticed. These alterations in staining occurred frequently within single muscle fibers. Evidence of capillary hemorrhage was usually present. Sections taken from noninfarcted areas in the same heart did not show these changes. This type of early degeneration (early hyalinization) of the myocardium has been observed in dogs when a chronic autonomic imbalance has been produced by prolonged administration of acetylcholine[6] or by prolonged stimulation of the vagus nerve.[7]

The alterations in the staining qualities became more pronounced within a few hours. By two and one-half hours (fig. 1 *A*) swelling of the muscle fibers was apparent. The nuclei also began to show changes in size and staining. The arterioles in the infarcted area appeared narrow but well filled with blood cells.

At ten hours (fig. 1 *B*) more marked degeneration was evident. Many leukocytes were scattered throughout the section. The muscle fibers were pale staining and showed a definite loss of striations. The nuclei were undergoing marked

6. Hall, G. E.; Ettinger, G. H., and Banting, F. G.: An Experimental Production of Coronary Thrombosis and Myocardial Failure, Canad. M. A. J. **34**:9, 1935.

7. Manning, G. W.; Hall, G. E., and Banting, F. G.: Vagus Stimulation and the Production of Myocardial Damage, Canad. M. A. J. **37**:314, 1937.

degenerative changes. All these changes were more advanced at the end of twenty-four hours, while at forty-eight hours early fibroblasts were seen growing into the infarcted area (fig. 2 *A*). The number of fibroblasts increased rapidly, as shown by the seventy-two hour section (fig. 2 *B*).

Sections taken from the infarcted region of the seven day specimen showed areas of complete necrosis surrounded by fibroblastic proliferation (fig. 3 *A*). Many small blood vessels were present. By the end of the second week the area of necrosis had become replaced by ingrowing fibroblastic tissue. The fibroblasts were now smaller and older, and the amount of intercellular matrix had increased.

Sections of an infarcted area taken twenty-two days after ligation showed fairly dense areas of scar tissue (fig. 3 *B*). The tissue was less cellular in appearance, and the fibroblasts were of the adult type. Typical bands of collagen made up the greater portion of the area.

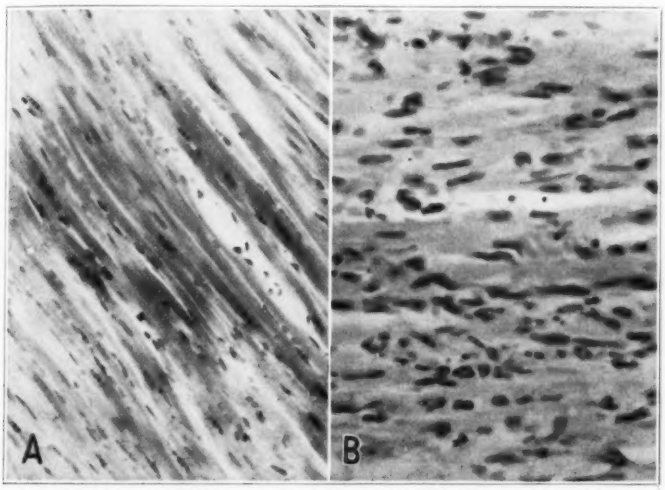

Fig. 1.—Portions of early infarcts. *A*, two and a half hours after ligation. *B*, ten hours after ligation.

Electrocardiographic Changes.—The typical changes which occurred after the sudden ligation of the anterior descending branch were an elevation of the RT segment in lead I (high take-off) and a depression in leads II and III (low take-off), indicative of infarction on the anterior surface or apical region of the heart. The depression of the ST segment, with a low take-off, in lead II was especially characteristic of this group. Progressive alterations in the contour and the direction of the T waves were observed in all cases. Ventricular extrasystoles were infrequently seen after the ligation. In only 1 case was there any evidence of axis deviation. This was in contrast to the common finding of left axis deviation with occlusion of the circumflex branch.

The changes in the RT segment of the ventricular complex, although sometimes marked, were frequently transient, and in many instances the electrocardiograms showed that the heart had become relatively normal within a few days. Records were taken in some cases nine months after ligation.

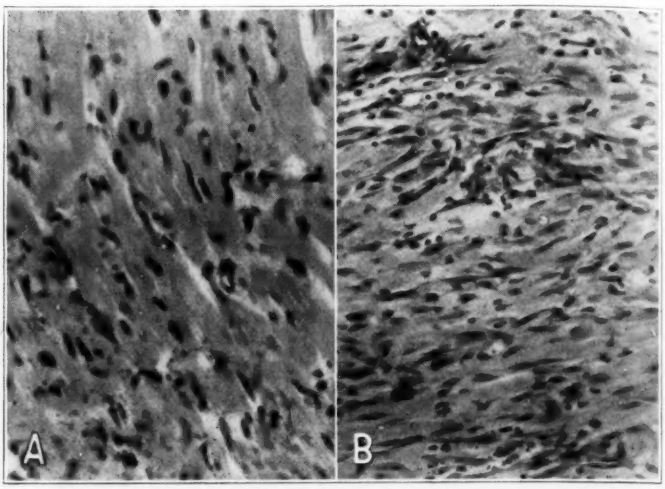

Fig. 2.—Portions of early infarcts. *A*, forty-eight hours after ligation. *B*, seventy-two hours after ligation.

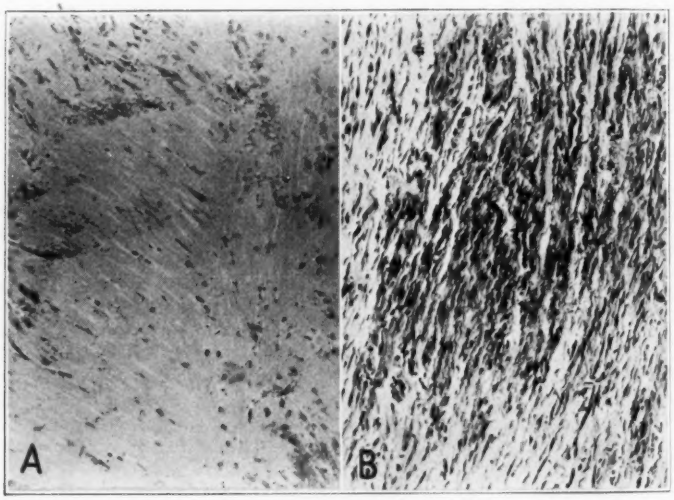

Fig. 3.—Portions of older infarcts. *A*, seven days after ligation. *B*, twenty-two days after ligation.

GROUP 2.—*Ligation of the circumflex branch of the left coronary artery during anesthesia.*

The circumflex branch was ligated in 23 dogs under morphine and ether anesthesia. Seventeen dogs survived and 6 died suddenly after the ligation.

Changes in Blood Pressure.—In the animals which survived the occlusion the changes in blood pressure were fairly uniform. In one dog the pressure fell from a normal of 120 to 80 mm. of mercury within two minutes of the occlusion and then gradually increased to 88 mm. of mercury in the next three minutes. This level was maintained for about fifteen minutes. Then a more marked decrease occurred, and the blood pressure went as low as 55. Cardiac irregularities were noted at this time (fig. 4). However, after a few minutes the pressure gradually increased, and twenty-two minutes after ligation it had returned to 100. The

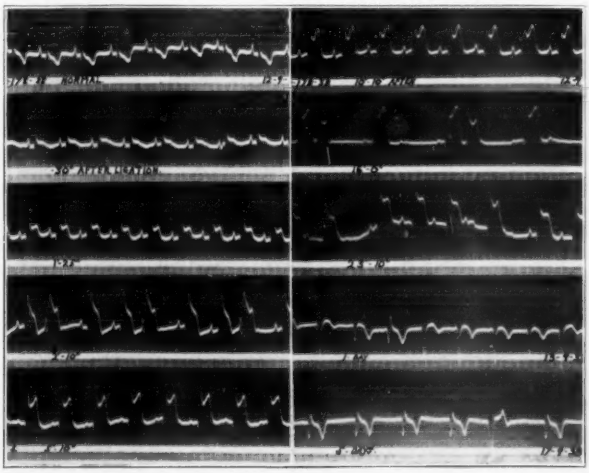

Fig. 4.—Lead II, showing progressive changes following acute ligation of the circumflex branch in the anesthetized dog. Note early elevation of the RT segment.

heart again became regular, and the pressure remained constant at 100 for at least thirty minutes longer.

The changes in blood pressure recorded for animals which did not survive the occlusion were likewise fairly uniform. In one dog the pressure fell to 80 within twenty-five seconds. This level was maintained for about six minutes, and then there was a sudden decrease to 40. This sudden drop coincided with the onset of ventricular fibrillation. Within a few seconds the blood pressure was zero.

Electrocardiographic Changes.—The electrocardiographic changes which occurred after sudden ligation of the circumflex branch in the anesthetized dog were typical for the animals which recovered, and typical changes were recorded for those which did not recover.

Alterations in the direction and the contour, as well as the amplitude, of the T wave occurred within thirty seconds of occlusion (fig. 4). There were progressive elevation of the ST take-off and disappearance of the isoelectric ST segment (leads II and III). This premonitory period may be very short or

extend over many minutes. The regularity of the heart was quickly disturbed by premature contractions of ventricular origin. This phase was coincident with the second fall in blood pressure. Infrequently partial block was evident, but this condition usually gave way to a series of extrasystoles.

In those animals which recovered the changes in the T wave persisted for about seven days and then showed a gradual altered inversion as the healing of the infarcted area progressed (figs. 1 to 3). Marked left axis deviation (fig. 5) was evident within twenty-four hours, and extrasystoles originating in the left ventricle were not infrequently found. The records indicated infarction of the posterior surface.

In the animals which died suddenly after the occlusion, the electrocardiogram showed an early alteration in the T wave and an elevation of the ST isoelectric segment in leads II and III. Single extrasystoles became apparent within a few seconds and were followed by definite groups of extrasystoles. Ventricular tachy-

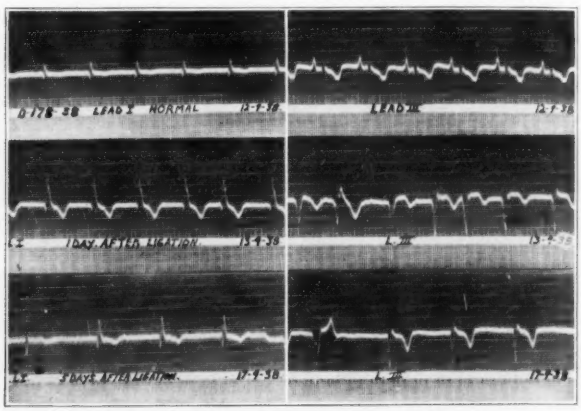

Fig. 5.—Leads I and III for the animal represented in figure 4, taken one and five days after ligation, showing left axis deviation.

cardia, simple or complex, invariably followed the phase of extrasystoles. In some records the tachycardia passed gradually into fibrillation, while in others the transition was more abrupt.

As indicated previously, the blood pressure fell to zero with the onset of fibrillation.

Pathologic Changes.—Immediate autopsy was performed on all dogs which died after the occlusion. The faint outline of the infarcted area could be distinguished, sometimes with difficulty, by the paleness of the area. No significant histologic changes could be detected.

The animals which recovered showed, when killed at a later date, changes in the heart muscle similar to those already described for corresponding time intervals in group 1.

Results.—In this group of 23 animals, in which the circumflex branch was ligated with the animal under morphine and ether anesthesia, 17 survived and 6 died suddenly after ligation. This indicates a probable mortality of about 25 per cent.

GROUP 3.—*Ligation of anterior descending branch of the left coronary artery in the conscious state.*

In the 22 animals in this group, at least twenty-four hours after operation and anesthesia the ends of the ligature protruding through the chest were pulled tightly. This produced a sudden occlusion of the anterior descending branch of the left coronary artery. Electrocardiograms were taken before, during and at varying intervals after the strings were tightened.

Clinical and Electrocardiographic Changes.—Typical signs of coronary occlusion, such as pain (indicated by whining and restlessness), dilated pupils and dyspnea, were observed. These signs were evident about sixty to ninety seconds after occlusion, and their appearance corresponded roughly with the onset of ventricular tachycardia. In 7 of the 22 dogs fatal ventricular fibrillation followed

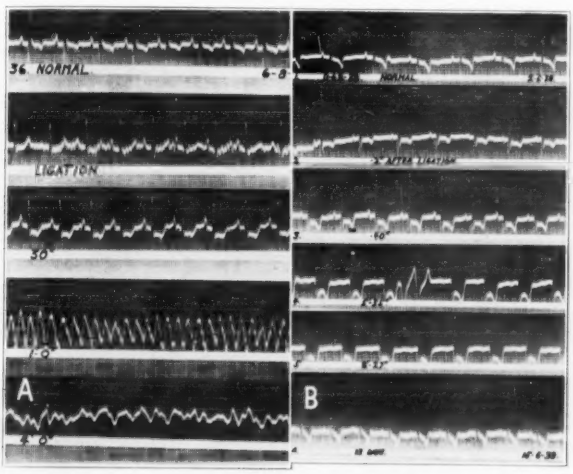

Fig. 6.—Lead II, showing changes following ligation of the circumflex branch of the left coronary artery in the conscious dog. Note early depression of the RT segment. *A*, fatal ventricular fibrillation. *B*, survival type of record.

the tachycardia (fig. 6 *A*). Two other dogs died unobserved within twelve hours. Typical signs of infarction of the anterior surface were present in the records for all 13 dogs which recovered. Earlier changes occurred in the form, the amplitude and the direction of the T wave and in the depression (leads II and III) and elevation (lead I) of the ST isoelectric segment (fig. 6 *B*).

Pathologic Changes.—Since the mortality in this group was 40 per cent, as compared with less than 10 per cent in group 1, in which ligation of the same branch was performed with the animals under anesthesia, it seemed reasonable to suppose that some mechanism was involved which was capable of being eliminated by the anesthesia.

Immediate autopsy was performed on 6 dogs which died suddenly after the ligation. Besides the area of ischemia produced by the arterial ligation, one or more smaller pale grayish areas were seen in other regions. These areas resembled

the primary infarcted area except in location and size. No such ischemic-looking areas were observed in the hearts of dogs dying as the result of acute ligation of a coronary artery performed while they were under anesthesia.

GROUP 4.—*Ligation of the circumflex branch of the left coronary artery in the conscious state.*

Sudden ligation of the circumflex branch was effected in 16 dogs twenty-four hours after the preparatory operation. Electrocardiographic records were obtained before, during and after ligation. In 5 animals continuous readings of the blood pressure were obtained. All 16 animals experienced pain, as evidenced by whining, restlessness, excitement and dilatation of the pupils. Twelve animals died suddenly after the ligation. This mortality of about 75 per cent is to be compared to that in group 2 (ligation with anesthesia), in which the mortality was about 25 per cent.

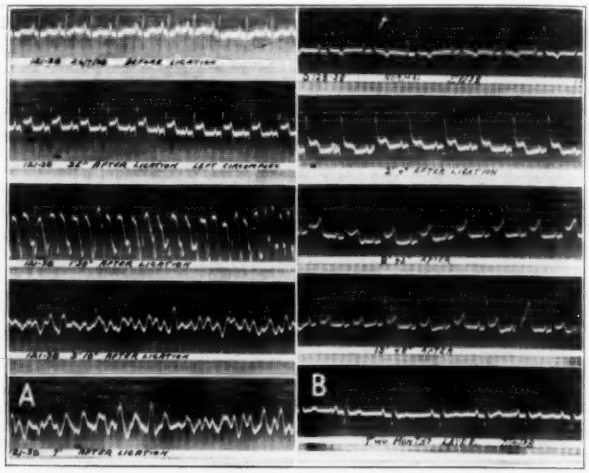

Fig. 7.—Lead II, showing changes following ligation of the circumflex branch in the anesthetized dog. In *A*, note early elevation of the RT segment, ventricular tachycardia and fatal fibrillation. *B*, survival type of record.

Changes in the Blood Pressure.—In a typical case the blood pressure fell from a normal of 120 to 100 within five seconds of the ligation. (This first decline in pressure was observed in all cases of sudden occlusion of the coronary artery.) The blood pressure continued to fall, reaching a level of 70 within seventy seconds. At this point a sudden decrease to about 40 occurred, coincident with the onset of ventricular fibrillation. The decline in blood pressure to zero was then rapid.

It will be recalled that in the animals surviving ligation of the circumflex branch produced while they were under anesthesia (group 2) a second fall in blood pressure was observed. In these dogs the second decrease coincided with the onset of cardiac irregularities which did not continue to fibrillation. With the return of the heart beat to normal rhythm the blood pressure returned almost to normal.

In the few surviving animals in group 4, the second fall in blood pressure also coincided with the onset of tachycardia, but as fibrillation did not intervene

the pressure gradually returned to normal with the reestablishment of a normal cardiac rhythm.

Electrocardiographic Changes.—The typical electrocardiographic changes which occurred in 75 per cent of the animals in this group are illustrated in a series of lead II records taken before and immediately after ligation (fig. 7 *A*). Within thirty-five seconds a marked elevation of the ST isoelectric segment (leads II and III), with a change in the amplitude and contour of the T wave, was evident. Extrasystoles were followed by the onset of ventricular tachycardia, which was well established in ninety seconds. Fatal ventricular fibrillation rapidly intervened and continued, with gradually decreasing amplitude, for as long as fifteen to thirty minutes after its onset.

The electrocardiographic changes which occurred in the surviving animals (25 per cent) also showed elevation of the ST isoelectric segment (leads II and III), changes in the T wave and extrasystoles (fig. 7 *B*). Ventricular tachycardia and fibrillation did not occur. The late interval records are similar to those of group 2.

Pathologic Changes.—The infarct produced by ligation of the circumflex branch differed from the one produced by ligation of the anterior descending branch only in location and size. In addition, one or more small ischemic-looking areas, independent of the primary infarct, were observed at autopsy. These areas, absent in the anesthetized dogs, also suggest that the higher mortality for the conscious animals is the result of a mechanism which is minimized by the anesthetic.

ADDITIONAL EXPERIMENTS.—In order to eliminatae the possibility that displacement and traction of the heart played some role in the increase of mortality following ligation of a branch of a coronary artery in conscious dogs, a series of animals was prepared as in group 4. After the chest was closed, but with the animal still under the anesthetic, sudden occlusion was produced by pulling the two ends of the loosely tied ligature. The mortality was the same as in group 2 (20 to 25 per cent), in which the ligation was completed in the open thorax with the animals under anesthesia.

COMMENT

In the dog the left coronary artery, after giving off deep septal branches, divides almost immediately into the anterior descending and the circumflex branch. The distribution of the anterior descending branch is comparable to that in the human being. The circumflex branch is, however, much the larger branch and supplies a greater area of the myocardium than either the anterior descending branch of the left or the right coronary artery. The circumflex branch supplies marginal and atrial branches and, continuing on to the posterior surface, becomes the posterior descending branch. In the human heart the posterior descending branch is the termination of the right coronary artery.

Thus, ligation of the circumflex branch of the left coronary artery produces infarction of a greater extent than ligation of any other branch, and electrocardiographic records after such ligation show evidence of posterior infarction. The right coronary artery, according to our experience, can be ligated without increasing the mortality beyond that expected in thoracic operations (less than 1 per cent). We have found also that

dogs in which the circumflex branch of the left coronary artery has been ligated while they were under anesthesia are relatively able to tolerate subsequent ligation of the right coronary artery. Similarly the right coronary artery can be fairly safely ligated in dogs which have had the anterior descending branch of the left coronary artery ligated while they were under anesthesia. None of the dogs survived when the third large branch was ligated at a later operation.

The collateral or anastomosing coronary circulation, as in the human heart, is much more abundant in the old than in the young. However, young dogs and pups, although this anastomosis is not nearly so well developed, are much more tolerant to occlusion of a large coronary artery than old dogs. This has been well illustrated in experiments during the past three years. For example, 2 old dogs in which the anterior descending branch of the left coronary artery was tied while they were under anesthesia died immediately after ligation, whereas many pups (3 months old) and young adult dogs readily survived this operation (90 per cent). It would seem, in general, that as the age of the animal increases the mortality following ligation of a coronary artery likewise increases. This possible complicating factor was eliminated in the present series by using young adult dogs in all groups, except in those cases specifically cited.

The experiments reported in this paper show, as others have previously shown, that large areas of the myocardium can be rendered ischemic by ligation of various branches of the coronary arteries in the anesthetized animal with a relatively low mortality. When similar ligations are performed in the conscious animal the mortality is greatly increased.

When the anterior descending branch of the left coronary artery is ligated in the anesthetized dog the mortality is less than 10 per cent. When the same branch is ligated in the conscious dog the mortality immediately increases to about 40 per cent. Similarly, when the circumflex branch is ligated in the anesthetized dog the mortality is about 25 per cent, while ligation of the same branch in the conscious dog is attended by a mortality of about 75 per cent, as shown in the accompanying table:

Mortality in the Four Groups of Experiments

Group	Branch Ligated	Anesthesia	No. of Dogs	Sudden Death				Delayed Death (Cardiac), 14 Days
				½ Hr.	12 Hr.	24 Hr.	Mortality, %	
1	Anterior descending	Yes	17	1	0	0	<10	0
2	Circumflex	Yes	23	5	0	1	25	0
3	Anterior descending	No	22	7	2	0	40	1 (rupture)
4	Circumflex	No	16	6	3	2	75	1 (cardiac failure)

The primary infarct produced is of course relatively the same size in the anesthetized and in the conscious animal. Why then is there such an increase in mortality for the conscious dog? This may be brought about through several mechanisms. Perhaps the sudden accumulation of metabolites, with an increase in lactic acid at the expense of glycogen, in the ischemic area sets up afferent sympathetic impulses. These may, in turn, initiate efferent parasympathetic vasoconstrictor impulses which produce spasm of the medium-sized and the smaller coronary arteries and arterioles. This mechanism would result in the production of relatively large areas of ischemia secondary to the primary infarcted area. Under these conditions disturbed conduction and contraction are inevitable, and extrasystoles, tachycardia and fatal fibrillation, in that sequence, might conceivably follow.

If the secondary ischemia were less, the disturbances would likewise be lessened and fibrillation might not be initated. Recovery would then be possible. The animals in groups 2 and 4 which did survive showed evidence of pain equal to that exhibited by the animals which did not survive. In the anesthetized condition, when pain could not be manifested, it is possible that such reflex spasm was prevented.

Additional support to the observation of reflex coronary artery spasm has been obtained in some preliminary experiments. A decrease in the rate at which blood flowed through the circumflex branch before, during and after sudden ligation of the anterior descending branch in the conscious animal was recorded in two instances. Whether this decrease was due to a reflex spasm of the distal arterioles or directly to the slight decrease in the mean diastolic pressure remains to be determined. Experiments will be presented in a future paper to show that the increase in mortality following ligation of a coronary artery in the conscious animal is not the result of changes in the systemic blood pressure.

From other preliminary experiments, in which smaller branches of the coronary arteries were ligated, it seemed that the apical region was the most sensitive to ischemia and that fibrillation was most readily produced when the blood supply to this region was decreased. Possibly this may be explained when more is known about the relation between the ventricular muscle bundles, the spread of electric activity through these muscle bundles and the factors which initiate the sequence of events which terminate in fatal ventricular fibrillation.

Although in these experiments fatal ventricular fibrillation occurred in all the animals which died suddenly after ligation of a coronary artery, it is possible that in a much larger series of experiments a few instances of sudden death from heart block would have been encountered. A few cases of sudden death from heart block, with actual electrocardiographic evidence, have been reported in the literature. The patients

were all known to have cardiac disease and perhaps had been receiving drugs, such as digitalis or quinidine.

Experimentally we [8] have shown that the administration of various drugs prior to acute ligation of a coronary artery in conscious animals diminishes the incidence of fatal ventricular fibrillation while increasing the incidence of fatal heart block.

SUMMARY

The mortality following sudden occlusion of the anterior descending branch of the left coronary artery in the anesthetized dog is less than 10 per cent. For the conscious dog the mortality is about 40 per cent.

For sudden occlusion of the left circumflex branch, the mortality is about 25 per cent with anesthesia and about 75 per cent without.

The great increase in mortality for the conscious animal may be the result of a reflex spasm of collateral arterioles and small arteries producing additional areas of ischemia.

All the animals that died suddenly after ligation in the conscious state showed evidence of ventricular extrasystoles, tachycardia and fibrillation in that sequence.

8. McEachern, C. G., and Hall, G. E.: Unpublished data.

ANGINA PECTORIS IN HEREDITARY XANTHOMATOSIS

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It has long been agreed that the various forms of xanthomatosis are of general medical interest and not simply the expression of a local change in the skin. In many cases deposits of the same structure as that of the cutaneous deposits occur in internal organs. In 1878 Quinquaud advanced the idea that xanthoma is due to changes in the blood, hypercholesteremia, and more recent investigations have established the fact that it does concern a disturbance of lipoid metabolism.

Other forms of lipoidosis, such as Gaucher's disease and Niemann-Pick disease, will not be considered at this time; neither will the xanthomatous manifestations in diabetes, myxedema, pregnancy and disease of the liver with icterus be discussed.

The constitutional nature of "essential" xanthomatosis is shown clearly by its hereditary occurrence. Török [1] observed xanthomatosis as a hereditary manifestation in several families, and this has since been confirmed by others. The localization of xanthoma in the internal organs, particularly in the biliary tract and the vascular system and notably in the coronary arteries and the cardiac valves, has been observed. Less frequent localization in various mucous membranes has been described also.

The earlier literature gives the impression that localization in the liver and biliary tract is more frequent and of greater clinical interest than localization in the vascular system. In 1873, however, Fagge [2] described a case of xanthomatosis with cardiovascular symptoms, and in 1889 Lehzen and Knauss [3] reported the case of a girl 11 years old in whom steadily growing xanthomatous nodules, with signs of mitral insufficiency, had been observed since her third year. The girl died suddenly, and postmortem study revealed extensive xanthomatous deposits in the aorta, with narrowing of the isthmus, as well as in other large arteries. Her sister, 9 years of age, also had cutaneous xanthomas.

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2. Fagge, C. H.: Tr. Path. Soc. London **24**:242, 1873.
3. Lehzen, G., and Knauss, K.: Virchows Arch. f. path. Anat. **116**:85, 1889.

Török [1] mentioned several fatal instances of xanthomatosis with cardiovascular disease. A number of subsequent observations of similar import have been published by various authors.[4] They concern mostly young persons or persons in their best years who died suddenly from heart disease, the anamnesis revealing other instances of the same nature in the families. In addition to xanthomas, hypercholesteremia has been demonstrated in many of these patients as well as in their relatives.

My attention was directed to this form of cardiovascular disease by the publications by Harbitz [4b] of his results of extensive and thorough studies of cases in Norway. In all previous publications about hereditary xanthomatosis associated with heart disease, the authors have seemed to take for granted that the condition is decidedly infrequent. I observed my first patient with xanthoma tuberosum and angina pectoris in April 1937, and by June I was able to make a preliminary report of a number of cases in which I expressed the opinion that hypercholesteremia is a frequent and important factor in heart disease.[5] This opinion has been strengthened beyond expectation by the study of additional patients, many of whom have been referred to me by my colleagues. The article by Montgomery [6] also has confirmed my opinion. He has discussed 26 cases of xanthoma tuberosum, in nearly half of which there were cardiovascular symptoms. In these cases and in 45 cases of palpebral xanthelasma, Montgomery demonstrated cholesteremia. He has stated that cardiovascular and other systemic disturbances are frequent in palpebral xanthelasma. He has also observed a frequent familial disposition in his cases.

In my cases the xanthomatous deposits occurred as xanthelasmas on the eyelids and as xanthoma tuberosum. Palpebral xanthelasma is the more frequent (fig. 1) and occurs oftener in women than in men. Not infrequently xanthoma tuberosum is present at the same time; and as these two deposits have the same structure, they may be regarded as external localizations of the same process. Xanthoma tuberosum appears as nodes of variable size and number on the extensor surfaces, most frequently on the fingers, the elbows, the tibial tuberosities and the achilles tendons and less frequently elsewhere (figs. 2 and 3). The nodes may be quite minute (fig. 4) and hence are easily missed. They are as a rule multiple and may be so large as to cause deformities and cosmetic

4. (*a*) Arning, E., and Lippmann, A.: Ztschr. f. klin. Med. **89**:107, 1920. (*b*) Harbitz, F.: Nôrsk mag. f. lægevidensk. **86**:321, 1925; **97**:695, 1936; **98**:1317, 1937; Tumors of Tendon Sheaths, Joint Capsules and Multiple Xanthoma, Arch. Path. **4**:507 (Oct.) 1927; Ueber plötzlichen Tod mit natürlicher (d. h. nicht gewaltsamer) Todesursache, insbesondere bei jungen Leuten, monograph 5, Norske Videnskapsakademi i Oslo, Matematisk-Naturvidenskapelig Klasse, 1938.

5. Müller, C.: Acta med. Scandinav., 1938, suppl. 89, p. 75.

6. Montgomery, H.: Proc. Staff Meet., Mayo Clin. **12**:641, 1937.

as well as mechanical disturbances (figs. 5 and 6). The consistency may vary greatly. Below the knee the hardness may simulate a bony overgrowth of the tibial tuberosity. The nodes do not infiltrate the skin, which retains its usual color; but if the skin is stretched, the yellow of the xanthoma may be seen. The nodes are usually lobulated or finely granular and intimately connected by infiltration with tendons, fascia or periosteum. The growth is slow and gradual.

The diagnosis of palpebral xanthelasma as a rule is easily made, but the condition may be overlooked, especially when the skin is wrinkled. Xanthoma tuberosum is differentiated without difficulty from Heberden's nodes and from deposits of uric acid but may be confused with the pads on the fingers described by Garrod.[7] These nodes (fig. 7) are composed of fibrous tissue and occur on the dorsal sides of the joints between the first and second joints of the fingers (never on the thumb). These pads are not uncommon and may occur in families.

Fig. 1 (case 13).—Xanthelasma of the eyelids.

It is noteworthy that in xanthomatosis, arcus senilis is frequent, even when the patients are young.

The xanthoma deposits contain cholesterol, 24.9 per cent of the dried mass; phosphatide phosphoric acid, 0.26 per cent, and fat, 20.4 per cent.[8]

Xanthoma tissue is composed of large, so-called foam cells, which contain lipoids; inflammatory cells of various kinds, including giant cells; products of the reaction of the tissue to the lipoid deposits, and in the latter stages connective tissue. It seems to be the general opinion that the arteriosclerotic lesions in xanthomatosis cannot be distinguished either grossly or microscopically from the lesions of common arteriosclerosis.

7. Garrod, A. E.: St. Barth. Hosp. Rep. **29**:157, 1893; Brit. M. J. **2**:8, 1904. White, H., and Hale: Quart. J. Med. **1**:479, 1907-1908.

8. Raeder, G.: Norsk. mag. f. lægevidensk. **97**:113, 1936.

Fig. 2 (case 17, family 5).—Xanthoma tuberosum. Besides the nodes on the elbows, fingers and knees, there were deposits also on the achilles tendons and xanthelasma of the eyelids.

Fig. 3 (case 1).—Xanthoma tuberosum of the achilles tendons.

The real cause of xanthomatosis and other forms of lipoidosis is not known; in fact, an understanding of this group of diseases is in its early stages. It is believed that the lipoids are deposited in the cells of the reticuloendothelial system.

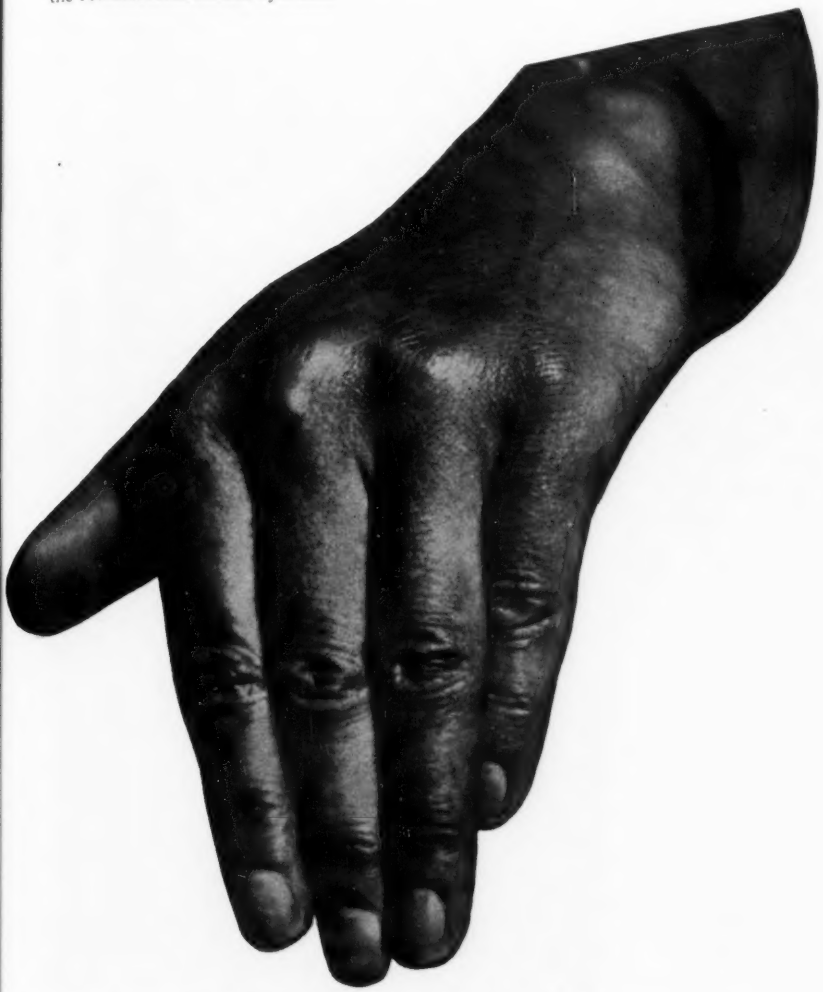

Fig. 4 (case 14).—Xanthoma tuberosum. In this case there was just one small node; it was on the extensor tendon of the middle finger.

REPORT OF CASES

The patients came from seventeen families. The members of these families who appeared to have been or to be affected by xanthomatosis, 76 in all, have been grouped as follows:

Fig. 5 (case 32).—Xanthoma tuberosum.

Fig. 6 (case 5).—Xanthoma tuberosum of the achilles tendons.

(*a*) The families in which xanthoma tuberosum, eventually also palpebral xanthelasma, occurred.

(*b*) The families in which palpebral xanthelasma occurred.

(*c*) The families in which there were no changes in the skin or subcutaneous tissue but in which the cardiovascular disease occurred in combination with hypercholesteremia and in which postmortem observations or other factors suggested that xanthomatosis might be the main cause of the cardiovascular disease.

Fig. 7.—Garrod's pads—fibrous nodules over the joints between the first and the second phalanges of the second and fifth fingers. These pads are hereditable.

Genetic charts are presented of families, many members of which have been studied (fig. 8).

Determination of the cholesterol content of the blood was made according to the Liebermann-Burchard colorimetric method as modified by A. Fölling. The normal limits are 100 to 200 mg. per hundred cubic centimeters. In every case duplicate analyses were made.

Families with Xanthoma Tuberosum and Angina Pectoris, Eventually Also Palpebral Xanthelasma.—FAMILY 1 (fig. 9).—A man (case 1) aged 45, an office worker, was admitted on April 13, 1937. When about 30 years old he noticed

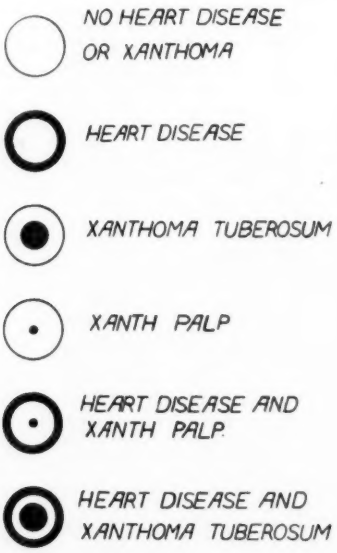

Fig. 8.—Key to the symbols employed in the following charts.

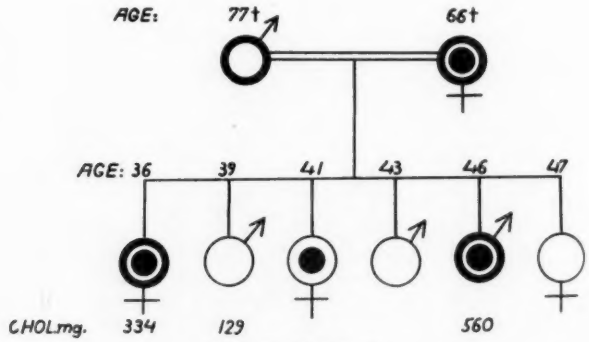

Fig. 9.—Family 1.

tender nodules on the dorsum of several fingers, on the elbows under the patellar ligament and on the achilles tendons (fig. 3). The nodules, almost symmetrically located, increased in size slowly and caused no disturbance except cosmetically. In 1932 a nodule was removed from the back of one finger, and microscopic sections revealed xanthomatous tissue. During the past ten years he had had

dyspnea on exertion and more recently typical attacks of angina pectoris, the pain stopping with rest or after the taking of glyceryl trinitrate. The electrocardiogram showed flattened T_1 and T_2 waves after exertion. In 1932 the blood content of cholesterol was 331 mg. per hundred cubic centimeters; in April 1937 it was 560 mg. per hundred cubic centimeters. The blood pressure was 125 systolic and 75 diastolic. The Wassermann reaction was negative. Roentgenographically the heart, the skull and the extremities were normal.

The patient's father and mother died of angina pectoris at the ages of 77 and 66 years, respectively. The mother (case 2) had nodules on the hands. Of the 5 siblings, 1 sister (case 3) 36 years old had the same cardiac symptoms on exertion as the patient. Examination of the heart and the electrocardiogram revealed no abnormality. Since her twenty-first year she had observed nodules, first on the heels and then on the elbows, under both knee joints and on the back of the second and third fingers of both hands. The cholesterol content of the blood was 334 mg. per hundred cubic centimeters. A second sister (case 4) had nodules on both heels but was otherwise well. The other siblings seemed well.

Comment.—A 45 year old man and his sister aged 36 years both suffered from angina pectoris with hypercholesteremia. A second sister had xanthoma tuberosum. The father and mother both died of angina pectoris; the mother had nodules on the hands.

FAMILY 2.—The first patient (case 5) in this family was a 76 year old man, an architect. I saw him first in 1935 on account of angina pectoris, from which he had suffered in increasing degree for sixteen years. At that time I did not associate the xanthomas, which he had had for forty years, with the angina. The blood contained 304 mg. of cholesterol per hundred cubic centimeters. The patient died of angina pectoris in June 1937. The xanthomas, which had grown slowly in the course of years, were unusually large (fig. 6).

This patient had 3 brothers and 7 half siblings on the father's side, all of whom were well except 1 full brother (case 6) 73 years old who had suffered from typical angina pectoris during the past six years. For about thirty years he had had nodules located much like those in case 5 but smaller. The cholesterol content of the blood was 440 mg. per hundred cubic centimeters. The heart was normal. The blood pressure was 150 systolic and 100 diastolic. The patient had 5 children, 1 of whom, a son (case 7) 39 years old, had complained of cardiac symptoms, but examination revealed only barely demonstrable thickenings over the terminal joints of the second and third fingers. The blood was not examined for cholesterol.

The first patient in this family (case 5) had 2 sons and 1 daughter. One son (case 8) had xanthoma tuberosum at both tibial tuberosities, and the daughter (case 9) had small xanthomatous nodules at the tibial tuberosities and on the dorsum of both long fingers. The sister showed a cholesterol content of the blood of 350 mg. per hundred cubic centimeters. Recently reports have been received to the effect that the second son has xanthoma nodules like those of his brother (case 8). The father (case 10) of 2 of the patients (cases 5 and 6) had larger nodes on the hands (about like those in case 5) and died of angina pectoris at the age of 58 years.

Comment.—A man 76 years old with xanthoma tuberosum and xanthomatosis died of angina pectoris about sixteen years after the disorders

were first noted. His father had xanthoma tuberosum and also died of angina pectoris. A son 41 years old and a daughter 36 years old both had xanthoma; the daughter showed hypercholesteremia (350 mg. of cholesterol per hundred cubic centimeters). A brother 73 years old had xanthoma, hypercholesteremia (440 mg. of cholesterol per hundred cubic centimeters) and angina pectoris, and his son had doubtful xanthoma nodules and mild anginal symptoms.

FAMILY 3.—A man (case 11) aged 59 years, a warehouse manager, had had symptoms of angina pectoris since his forty-eighth year. These were still quite typical after exertion. The blood pressure was 160 systolic and 115 diastolic. The heart was hypertrophic. The cholesterol content of the blood was 386 mg. per hundred cubic centimeters. Xanthoma nodules were present on the fingers, the

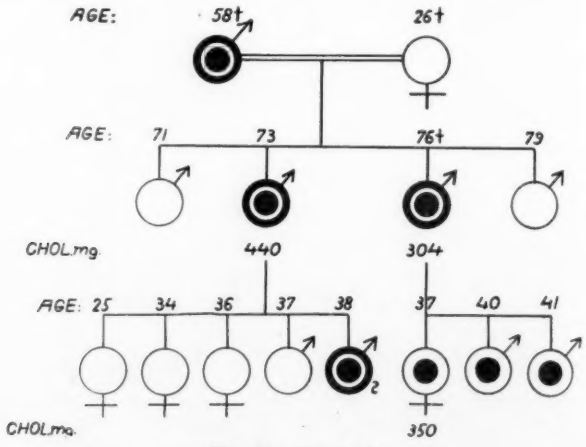

Fig. 10.—Family 2.

left olecranon, the tibial tuberosities and the achilles tendons. A photograph of his mother (case 12), who died in her seventy-third year, showed typical nodules on the hands. For several years before she died she had had pains in the chest.

FAMILY 4 (fig. 11).—A woman (case 13) aged 67, a widow, had had pain in the cardiac region on exertion for more than ten years. In 1937 the blood pressure was 185 systolic and 100 diastolic. There was a systolic murmur over the apex of the heart. Extrasystoles were noted. The electrocardiogram indicated a pathologic condition. For seventy-two hours before admission to the hospital on Jan. 4, 1938, she had suffered severe pain in the chest, and on entry the condition was typical of cardiac infarct with collapse (blood pressure, 110 systolic and 72 diastolic). The blood contained 262 mg. of cholesterol per hundred cubic centimeters. Xanthelasmas were present on all the eyelids (fig. 1), and xanthoma nodules were present on the fingers, the tibial tuberosities (fig. 12) and the heels. The patient died after a week. At autopsy (Dr. E. Waaler) yellow nodules were noted at the sites just mentioned. The heart weighed 620 Gm. The

valves were normal. The coronary arteries were everywhere sclerotic, with yellow spots and plaques; in the circumflex branch of the right coronary artery, about 4 cm.

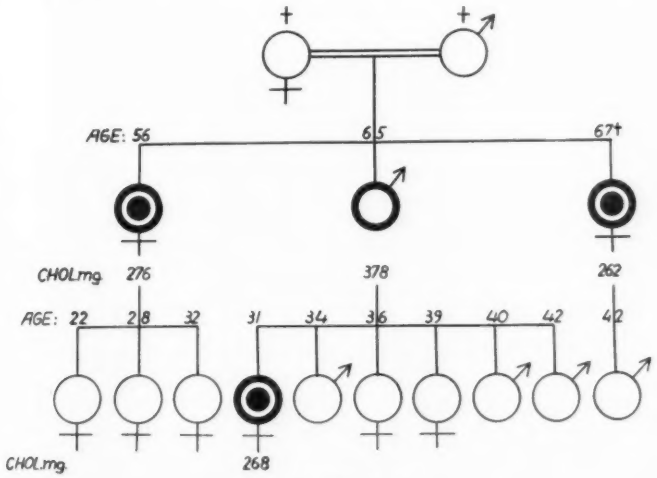

Fig. 11.—Family 4.

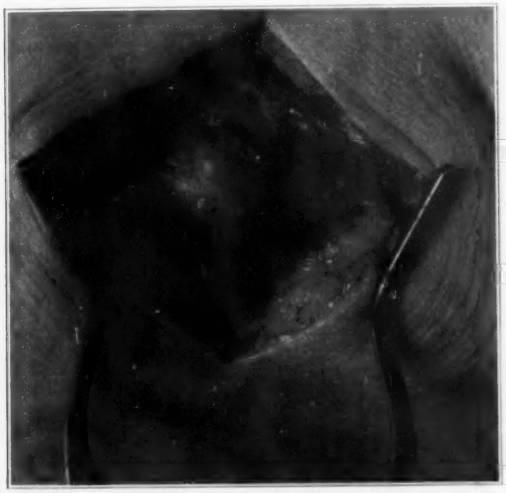

Fig. 12 (case 13).—A xanthomatous node below the knee. It was hard and might easily have been mistaken for an enlarged tibial tuberosity.

from its origin, was a thrombus. The posterior wall of the left ventricle was the seat of an infarct, about 6 by 4 cm. in size, with hemorrhagic borders. The aorta was markedly atherosclerotic (fig. 13), and the pulmonary artery showed yellow deposits (fig. 14). Xanthomatous deposits were present in the upper part of the

small intestine, being pea-sized yellow raised spots. In the left kidney was a well circumscribed hypernephroma.

The patient's father died at an early age of "inflammation of the bowels," and her mother died of cancer of the stomach. The patient's son, aged 42 years, was in

Fig. 13 (case 13).—The aorta.

good health, but her sister (case 14) and her brother (case 15) were not. The sister, aged 56 years, had had anginal symptoms for many years. An attack of rheumatic fever in 1925 had left no obvious effects on the heart. On the back of the left hand was a xanthoma tuberosum (fig. 4). The cholesterol content of the blood was 276 mg. per hundred cubic centimeters. The electrocardiographic

changes in this case greatly resembled those in case 13. In both cases ST_1 and especially ST_2 were deflected below the isoelectric line, and there were extrasystoles of the same type. The patient had 3 daughters (22, 28 and 32 years, respectively); the oldest one had "a nervous heart." The brother (case 15), 65 years of age, a coal dealer, had noticed for many years that he became short of breath when climbing a hill or stairs but was otherwise in good health until October 1937, when he had a severe attack of pain in the region of the heart lasting about twelve hours. Since then he had had pains in the elbows and in the chest on walking. There was no external evidence of xanthomatous deposits. On Sept. 16, 1938, the cholesterol content of the blood was 378 mg. per hundred cubic centimeters. Over the lower part of the sternum there was a systolic murmur. The blood pressure was 140 systolic and 110 diastolic. The electrocardiogram was abnormal.

The patient had 6 children, all apparently well save the youngest, a married woman 31 years old (case 16), who gave a ten year history of attacks of pain in

Fig. 14 (case 13).—Whitish yellow spots in the pulmonary artery.

the cardiac region, radiating into the back only. There was no dyspnea. Glyceryl trinitrate was reported to relieve the pain. Four years before, during pregnancy, a xanthelasma appeared on the left upper eyelid and a xanthomatous nodule on the back of the right hand. The blood pressure was 125 systolic and 85 diastolic. There was no enlargement of the heart, and the electrocardiogram was abnormal. On September 16 the blood contained 268 mg. per hundred cubic centimeters of cholesterol.

Comment.—Two sisters 67 and 56 years of age, respectively, and a brother 65 years old had angina pectoris and hypercholesteremia (262, 276 and 378 mg. of cholesterol per hundred cubic centimeters, respectively). The sisters had xanthoma tuberosum, and the elder one had palpebral xanthelasma. This sister, who had hypertension, died of cardiac infarction. There was extensive atherosclerosis of the aorta and of the pulmonary artery; there were also xanthomatous nodules in the

small intestine. The brother, who showed no signs of external xanthomatosis, had 6 children. One daughter 31 years old presented xanthelasma on the left eyelid, xanthoma tuberosum on the right hand and hypercholesteremia (286 mg. of cholesterol per hundred cubic centimeters). For about ten years she had had cardiac pain on exertion. The most remarkable feature of the disorder in this family seemed to be that the highest cholesterol content of the blood was found in the patient who had no changes in the skin.

FAMILY 5.—A man (case 17) aged 51, a shipping agent, had pneumonia in 1917 and icterus and nephritis eight or ten years before entry. He had rheumatic fever four or five times between 1911 and 1930. For many years he had had nodules on the hands, elbows, knees, heels and eyelids (fig. 2). Repeated efforts had been made to remove the palpebral deposits, but they had always returned. During

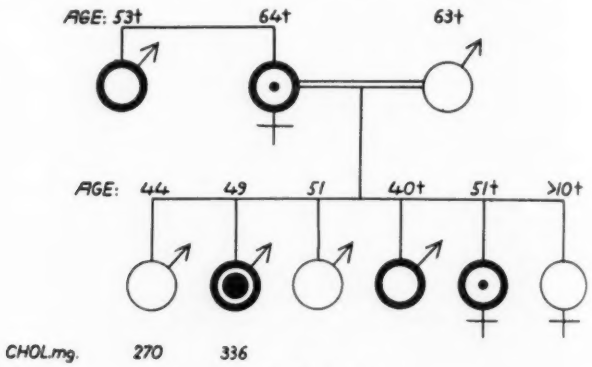

Fig. 15.—Family 6.

the last ten years he had had palpitation and dyspnea on walking and in the course of the last three months precordial pains radiating to the left arm. The pain came on only on walking and disappeared when he remained quiet or took glyceryl trinitrate. On June 6, 1938, the blood pressure was 130 systolic and 90 diastolic. There was no enlargement of the heart. A weak systolic murmur was heard over the apex; the electrocardiogram was abnormal. The cholesterol content of the blood was 435 mg. per hundred cubic centimeters. There were large, intensely yellow xanthelasmas on both lower eyelids and xanthomas of varying consistencies on the fingers and elbows, about the knees anteriorly, on the achilles tendons and along the dorsum of each foot. There was no history of xanthomatosis in these cases. Of the 3 siblings, a sister (case 18) has xanthelasma of the eyelids, but whether she has nodules elsewhere is not known.

FAMILY 6 (fig. 15).—A man (case 19) aged 49, an agent, suffered with a gastric ulcer from 1920 to 1922 but was otherwise well until eight or ten years before entry, when exertion was followed by constricting pain across the chest and into the arms which subsided with rest. These attacks had become worse, and he

had had to give up rowing, skiing and other activities and had had to move slowly even on flat ground. On Sept. 26, 1938, the blood cholesterol value was 336 mg. per hundred cubic centimeters. The electrocardiogram was abnormal (infarction). The right upper eyelid showed a small yellow deposit, the right hand a small thickening on the back, and the tibial tuberosities typical xanthomas.

In her last years the patient's mother (case 20) had cardiac pains and dyspnea. There is reason to believe that she had palpebral xanthelasma. She died at 63 of heart disease. She had 3 brothers and 3 sisters. Two of the brothers were well; the younger one (case 21), 44 years of age, was examined; the blood cholesterol value was 270 mg. per hundred cubic centimeters. The third brother (case 22) died suddenly at 40 years of age; he had suffered from angina pectoris, but whether he had xanthelasma or xanthoma is not known. There was a positive reaction to the Wassermann test of the blood. One sister (case 23) died suddenly in 1937, at the age of 51 years, after having had clinically typical angina pectoris for some time. She also had xanthelasma on all the eyelids. Prof. H. Salvesen had charge of the two last-mentioned patients (cases 22 and 23) and found that both had typical angina pectoris without hypertension, physical examination of the heart revealing no abnormality.

The uncle (case 24) on the mother's side of 1 patient (case 19) was 53 years old when he died suddenly while sitting in an automobile.

Comment.—A man aged 49 years with xanthoma tuberosum and hypercholesteremia (336 mg. of cholesterol per hundred cubic centimeters) had angina pectoris. His mother had died at the age of 64 of heart disease and had had palpebral xanthelasma. A brother and a sister of the patient both died suddenly, at 49 and 51 years, respectively, after having had angina for several years. The sister had extensive palpebral xanthelasma. The patient's maternal uncle also died suddenly. One of the patient's brothers, 44 years old, has cholesteremia.

FAMILY 7.—A married woman (case 25) aged 38 was referred to me by Dr. Scott Mathiesen, who had removed xanthelasmas from her eyelid. These appeared in January 1937 after a cold. There was a soft nodule about the size of a hazelnut on each achilles tendon. She had rheumatic fever in 1935; the heart did not seem to be affected. I examined her on May 24, 1938. She said she felt well, became a little short of breath on exertion but went swimming, cycling and skiing. There was a weak systolic murmur at the apex of the heart. There was no enlargement. The electrocardiogram was normal. The blood pressure was 120 systolic and 80 diastolic. The cholesterol value of the blood was 500 mg. per hundred cubic centimeters. On September 20 she consulted me again. Early in July an attack of severe pain in the chest set in as she was cycling homeward in a hurry on account of rain. After that she had similar but less acute pain after much less severe exertion. The pains had not radiated into the arms. The heart seemed normal. The blood pressure was 120 systolic and 65 diastolic. The cholesterol value of the blood was 438 mg. per hundred cubic centimeters. The palpebral xanthelasmas had returned. Her 4 children, 8 to 18 years old, were all well. Of her 4 siblings, 2 had died (pneumonia and brain tumor, respectively), and 2 were well. Her father, a physician aged 76, had had angina pectoris since about the age of 60; her mother (case 26) had died suddenly on the street, having had angina pectoris during the previous year; she was said to have had palpebral xanthelasma. The patient's grandmother (case 27) died suddenly of heart disease at the age of 57.

FAMILY 8 (fig. 16).—An unmarried woman (case 28) aged 42, an office assistant, was referred to me by Dr. Scott Mathiesen. She had influenza in 1918 and anemia with achylia gastrica in 1922. In 1923 a physician found that she had heart disease, but there were no special symptoms until in February 1938, when attacks of pain in the cardiac region, radiating into the chest, the back of the neck and the top of the larynx, appeared when she was walking. The attacks ceased when she stopped walking and took glyceryl trinitrate. Xanthelasma palpebrarum was present, and there were also hard nodes at the tibial tuberosities. The blood pressure was 130 systolic and 90 diastolic. The area of cardiac dulness was increased; there were systolic and diastolic murmurs at the apex. The cholesterol value of the blood was 305 mg. per hundred cubic centimeters. The patient had 3 living brothers and 1 sister, 36 to 42 years of age. One of the brothers (case 29), 41 years old, had had typical palpebral xanthelasmas which had disappeared spontaneously. The cholesterol value of the blood was 235 mg. per hundred cubic

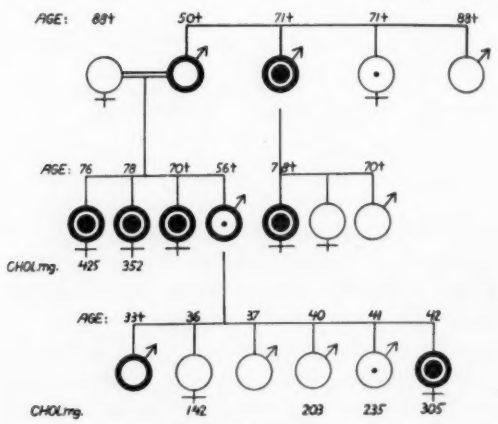

Fig. 16.—Family 8.

centimeters. There were no signs of heart disease or xanthomatosis in the other brothers (1 had a cholesterol value of 203 mg. per hundred cubic centimeters) or in the sister (the cholesterol value was 129 mg. per hundred cubic centimeters). One brother (case 30) died at the age of 33 of heart disease; he had had rheumatic fever several times, and autopsy showed chronic rheumatic endocarditis and pericarditis as well as calcification of the mitral valves. I obtained this information from Dr. R. Hatlehol. The father (case 31) of these siblings died suddenly at 56 of angina pectoris. He had palpebral xanthelasma. Of his 3 sisters, the youngest (case 32) presented herself for examination. She was 76 years old and unmarried. Since about the age of 70 she had suffered from pain over the sternum and extending into the neck and both arms to the wrists. The pain came on with walking and especially soon after eating but disappeared with rest. Since about 45 years of age she had had palpebral xanthelasma and nodules on the back of the fingers (fig. 5), elbows and heels. The nodules had grown slowly. The heart was apparently normal. The blood pressure was 150 systolic and 85 diastolic. The cholesterol value of the blood was 425 mg. per hundred cubic

centimeters. I had the opportunity of seeing the next youngest sister (case 33), aged 78 years. Six years previously she had herpes zoster in the left shoulder; otherwise she had enjoyed good health until about two years ago, when she began to have attacks of precordial pain when she walked or did heavy housework, but the pain disappeared with rest. The blood pressure was 150 systolic and 75 diastolic. The cholesterol value of the blood was 352 mg. per hundred cubic centimeters. Xanthelasma of the lids was barely visible. There were xanthomatous deposits (noticed first when she was in her fifties) on the fingers, tibial tuberosities and achilles tendons. The heart was somewhat enlarged toward the left, and there was a systolic murmur over the apex.

The third sister (case 34), the oldest, died of heart disease at 70, having had pains in the chest, xanthelasmas and xanthomas.

The father of these 4 patients died suddenly when running to catch a train. He had 2 brothers and 1 sister. One brother, the oldest of the 3, died at 88, the cause being unknown. The next oldest (case 36), the sister, also died of unknown cause at 71, having had large palpebral xanthelasmas. The other brother (case 37) died at 71 suddenly on the way to his office; he had nodules on the hands as well as xanthelasmas. This brother had 3 children, but nothing is known about them except that the youngest, a daughter (case 38), died of heart disease at 78. Professor Harbitz, her physician, told me that she had extensive arteriosclerosis, large palpebral xanthelasmas and nodules on the hands.

Comment.—In this family in three generations xanthomatosis and heart disease occurred in 7 persons, only xanthelasma in 2 and heart disease without any changes in the skin in 2. In the 9 cases of heart disease the indications were that angina pectoris occurred in 7, 3 patients dying suddenly. In 4 members with signs of xanthomatosis, hypercholesteremia was noted (235, 305, 352 and 425 mg. of cholesterol per hundred cubic centimeters, respectively). In 2 others, who seemed to be well, the cholesterol values were 203 and 142 mg. per hundred cubic centimeters, respectively.

Families with Palpebral Xanthelasma and Angina Pectoris.—FAMILY 9.—A widow (case 39) aged 64 had been well until February 1937, when she became dyspneic and felt pressure in the throat on walking up hill. A physician prescribed glyceryl trinitrate, which seemed to help her. On March 27, 1938, she suffered a severe attack of pain in the chest which lasted for two hours, with dyspnea. There was palpebral xanthelasma. The cholesterol value of the blood was 270 mg. per hundred cubic centimeters. The electrocardiogram showed infarction of type "T_1"; no enlargement of the heart or murmurs were noted. The patient died suddenly on Sept. 2, 1938, without any marked change in her general condition. Her parents died of unknown causes; a sister aged 70 had diabetes; a brother aged 68 was well.

FAMILY 10.—From 1928 to 1930 I had under my care a married woman (case 40) aged 55 years who had angina pectoris and xanthelasmas on all the eyelids. The angina began in February 1928, and the xanthelasmas were noticed first in 1922. She at present is under the care of Dr. Olaf Römcke, of Drammen, Norway, who has informed me that the xanthelasmas now surround both eyes and that the angina, which is alleviated by glyceryl trinitrate, remains about as in 1928. The cholesterol value of the blood in October 1938 was 454 mg. per hundred cubic

centimeters. In the electrocardiogram, T_1 was flattened and T_2 negative. Of the patient's 6 siblings, 3 died while young, 1 boy died of heart disease at 14; a brother (case 41) died of heart disease at 60; the surviving brother (50 years old) is well. The surviving sister (case 42), who is 53 years old, has xanthelasma about both eyes and anginal symptoms. Her heart is apparently normal. The cholesterol content of the blood was 535 mg. per hundred cubic centimeters in October 1938. The mother (case 43) of these patients died at 54 of angina pectoris; she had palpebral xanthelasma.

FAMILY 11 (fig. 17).—A married woman (case 44) aged 68 was under my care for several years on account of angina pectoris. In June 1937 she reported that she was worse. I then noted xanthelasma on the upper left eyelid; this had been present at least thirty years. About twenty-five years previously a similar spot

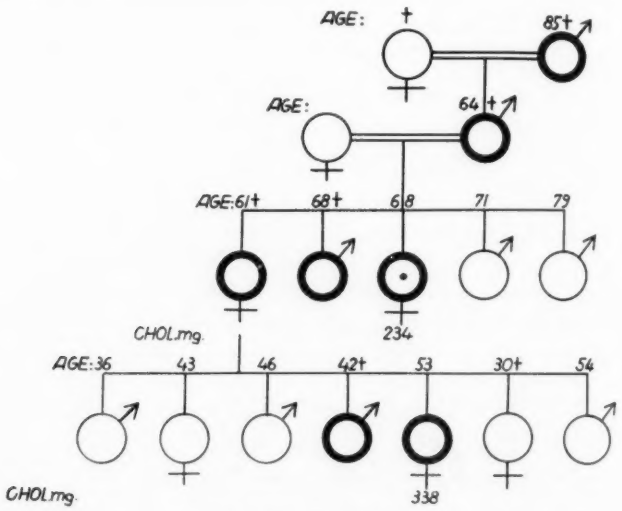

Fig. 17.—Family 11.

had been removed from the right upper lid. There were doutbtful xanthomatous deposits on the fingers. The blood pressure was 140 systolic and 95 diastolic. The cholesterol content of the blood was 234 mg. per hundred cubic centimeters. The electrocardiogram suggested previous myocardial infarction.

The paternal grandfather (case 45) and the father (case 46) died of angina pectoris, at 85 and 64 years of age, respectively; a sister (case 47) and a brother (case 48) also died of angina pectoris, at 61 and 68 years, respectively. I treated the sister, who had anginal symptoms for many years and died of cardiac infarct. I am unable to say whether she had any cutaneous deposits. Her son (case 49) came under my observation a few years ago; he was then about 40 and complained of typical anginal symptoms; he died suddenly at the age of 42. The cause of the angina in this case was discussed with Dr. Olaf Bang, who referred the patient to me; now, when the case is considered in the light of the family history, the cause seems plain enough. Finally, the last patient had a sister (case 50), 53 years

old at the time of writing, who had presented signs of mitral stenosis since youth and more recently had possibly presented signs also of aortic stenosis, but without the history of any infectious disease as a basis. She has hypercholesteremia (338 mg. of cholesterol per hundred cubic centimeters); there are no signs of xanthomatosis.

Comment.—In four generations of this family there have occurred 7 instances of heart disease, mostly of angina pectoris. Two of these patients showed hypercholesteremia (234 and 338 mg. of cholesterol per hundred cubic centimeters, respectively), and 1 had palpebral xanthelasma.

FAMILY 12 (fig. 18).—Dr. H. G. Dedichen referred to me a widow (case 51) 79 years old with aortic insufficiency, angina pectoris, hypertension, palpebral xanthelasma and hypercholesteremia (225 mg. of cholesterol per hundred cubic

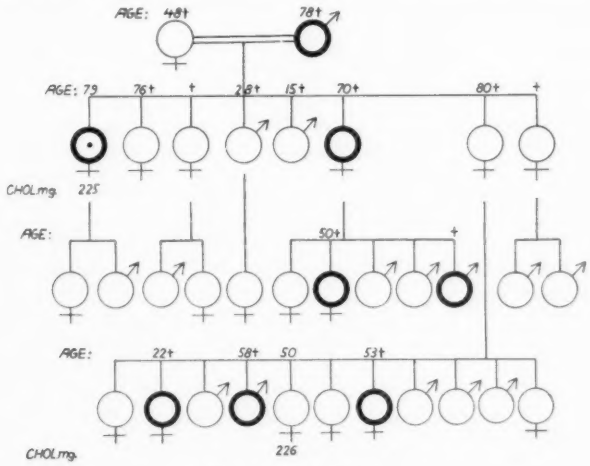

Fig. 18.—Family 12.

centimeters). The electrocardiogram showed bundle branch block of the usual type. The Wassermann reaction was negative. She had rheumatic fever when 12 to 14 years old. In three generations of her family, 7 members died of heart disease, 4 of them suddenly. The father (case 52) died suddenly at the age of 78; the mother died of typhoid at 52; a sister (case 53) died suddenly at 70 of heart disease while sleeping, her daughter (case 54) aged 50 died on the street while on her way to her physician because she had pains in the cardiac region, and her son (case 55) died of cardiac disease.

The next oldest of the 6 sisters (case 51) died at 80 of unknown cause. She had 11 children, among them 2 daughters (cases 56 and 57) and a son (case 58) who died of heart disease at 22, 53 and 58 years, respectively. Of these siblings, 1 survivor is a woman aged 50 who has no cutaneous deposits or sign of heart disease. The cholesterol content of the blood is 226 mg. per hundred cubic centimeters.

FAMILY 13.—A married woman (case 59) 41 years old had yellow spots on all her eyelids which returned after being removed twice. She had had anginoid pains as long as she could remember but not typical angina pectoris. The heart appeared normal on examination; the cholesterol content of the blood was 270 mg. per hundred cubic centimeters. Her mother (case 60) aged 65 complained of dyspnea and had to walk slowly. She had yellow spots on both upper lids. Her maternal uncle (case 61) died suddenly on the street at 65 years of age; 1 sister (case 62) died of heart disease at 52; her husband (case 19), not a blood relation, was a member of family 6.

FAMILY 14.—A married woman (case 63) aged 55 had noticed a yellow spot on the right upper eyelid for two years; it appeared soon after an attack of biliary colic. For six years she had had dyspnea on exertion and a disturbed heart action. On Feb. 19, 1938, a cerebral embolism caused paresis of the left side and difficulties of speech. On March 3 there was typical mitral stenosis with auricular fibrillation. The cholesterol content of the blood was 235 mg. per hundred cubic centimeters. The electrocardiogram indicated a pathologic condition. There was no family history of heart disease or of xanthomatosis.

Families with Probable Xanthomatosis and Angina Pectoris Without Xanthoma or Xanthelasma.—FAMILY 15.—A man (case 64) aged 58 for about a year had had a burning sensation behind the sternum and a tender spot under the left clavicle, especially after physical exercise. In April 1927 the heart was normal, the blood pressure was 140 systolic and 90 diastolic, and the electrocardiogram showed infarction of "type T_1." The blood cholesterol was 300 mg. per hundred cubic centimeters. He died after an automobile accident, with multiple cerebral hemorrhages, extensive atherosclerosis in the aorta (fig. 19) and pulmonary arteries, and myocardial fibrosis (autopsy by Dr. E. Waaler). The patient's brother (case 65) aged 65 consulted me in April 1937 on account of pains in the chest for three years. Since 1914 he had been treated for syphilis. The Wassermann test gave a negative reaction. The blood pressure was 220 systolic and 110 diastolic. The cholesterol content of the blood was 263 mg. per hundred cubic centimeters. There was accentuation of the second aortic sound. The electrocardiogram showed an abnormal condition. This patient's daughter (case 66) aged 35 was examined on Oct. 1, 1938, and was found to have mitral stenosis and hypercholesteremia (338 mg. of cholesterol per hundred cubic centimeters). A sister (case 67) of the 2 brothers died at 47 of heart disease associated with violent pain. There have been several cases of heart disease among relatives of the mother.

FAMILY 16.—A married woman (case 68) aged 59 had transitory angina pectoris in her forty-seventh year, the symptoms reappearing in her fifty-seventh year, followed in about half a year by cardiac infarction (type T_1) and then signs of cerebral embolism. She continued to have angina on exertion, hypertension and hypercholesteremia (273 mg. of cholesterol per hundred cubic centimeters). Both parents had cardiac symptoms, the mother (case 69) dying of angina pectoris, as did also the sister (case 70), at the age of 60; a second sister (case 71), who was 50 years old, had had symptoms like those of the patient. There was no history of xanthomatosis in the family.

FAMILY 17.—Two brothers (cases 72 and 73) had cardiac infarction of type III at 44 and 38 years of age, respectively. Both had hypercholesteremia (300 and 214 mg. of cholesterol per hundred cubic centimeters, respectively), as did also an insane sister (case 76), who otherwise seemed well (222 mg. per hundred cubic centimeters). The mother (case 74) died of heart disease at 57 and the father (case 75) of heart disease with dropsy.

COMMENT

The foregoing histories deal with 76 persons (32 men and 44 women) of interest to the subject of this paper. I have myself examined 33 of

Fig. 19 (case 64).—The aorta.

these persons; concerning the rest I have given the information that I have obtained from others. The ages varied from 31 to 85 years, the average for the living members being 56.3 years and for the deceased ones 60.9 years. Most of these persons were office workers or teachers.

The laboring class was not represented, in spite of the fact that most of my patients come from that class.

Of the 76 persons, 68 appeared to have had heart disease, while 8 had xanthelasma only. Of the 68 persons, the diagnosis of angina pectoris seemed indicated in 59, of whom 38 have died, 14 suddenly; in 11 cases signs of cardiac infarction were found, and 3 of these persons have died. In 11 cases heart disease was reported but without information as to its nature; presumably 5 have had valvular lesions. In 6 of the 33 patients I examined hypertension (160 systolic or more) was found. Syphilis was mentioned in the history in 2 cases, but the Wassermann reaction was negative. No positive reaction to the Wassermann test was obtained, but the test was made in only a small number of cases. Five of the patients had had acute rheumatic fever, and in 1 case (case 30) death no doubt resulted from rheumatic carditis. Case 51 concerns a woman 79 years old who had rheumatic fever when 12 or 14 years old and now has signs of aortic insufficiency and typical angina pectoris. The 3 other patients who had had rheumatic fever had no valvular disease but showed signs of angina pectoris; presumably they did not have rheumatic heart disease.

In the seventeen family histories xanthoma tuberosum was noted alone or combined with xanthelasma in 8 families; in six families there were records of xanthelasma only; in 3 there were no records of cutaneous changes. Cutaneous xanthomatosis in one form or another occurred in 38 persons, xanthoma tuberosum in 24 and xanthelasma in only 14; 10 had both forms at the same time. Undoubtedly instances of xanthomatosis have been missed because the persons were not examined or because they were examined before I knew about its significance.

The quantity of cholesterol in the blood was estimated for 37 patients; the amount varied from 129 to 560 mg. per hundred cubic centimeters. In all except 2 cases hypercholesteremia was found, and in these 2 cases there were no signs of xanthomatosis or heart disease. Of persons who had neither sign of heart trouble nor xanthomatosis, it was possible to obtain specimens of blood from only a small number; hence there is no way of knowing how many of the apparently well persons had hypercholesteremia and were hereditarily predisposed to it. The cholesterol content of the blood in the remaining 35 persons was as follows: Eight had 200 to 250 mg.; 10, 251 to 300 mg., and 17, more than 301 mg., per hundred cubic centimeters. Hypercholesteremia, in some cases severe, consequently is commonly found. In 16 instances of xanthoma tuberosum, with or without xanthelasma, the average cholesterol content of the blood was 362 mg. per hundred cubic centimeters, in 8 instances of xanthelasma only the average was 307 mg. per hundred cubic centimeters and in 13 instances of external xanthomatosis the average was 256 mg. per hundred cubic centimeters. Thus,

hypercholesteremia is most marked in connection with xanthoma tuberosum, but there seems not to be any definite relation between hypercholesteremia and deposits in the skin. In family 4, for instance, the highest content (378 mg.) was obtained in case 15, in which there were no cutaneous changes, but for the patient's sisters (cases 13 and 14), both with xanthoma tuberosum, the values were lower—262 and 276 mg. per hundred cubic centimeters, respectively. Neither does it appear that there is any definite relation between the cardiovascular changes and the degree of hypercholesteremia. Thus, for 7 persons who were apparently normal except for palpebral xanthelasma and whose family records showed no heart disease, the cholesterol content of the blood was 300 mg. per hundred cubic centimeters. These patients are not included in my case reports.

The reports I have presented confirm the previous observations on xanthomatosis as a cause of hereditary heart disease. They reveal further that the syndrome of cutaneous xanthomatosis, hypercholesteremia and angina pectoris presents itself as a well defined clinical disease entity in the first, second, third and fourth generations, that is, as a dominant hereditary disease. There can be hardly any doubt but that xanthomatous deposits in the coronary artery and consecutive myocardial ischemia are the cause of the angina pectoris. That the disease may cause changes in the mitral and aortic valves is shown in earlier observations, both clinical and anatomic, as illustrated perhaps by cases 28, 50, 51, 63 and 66.

The case reports also show—and this is an important clinical observation—that the form of angina pectoris under discussion may occur in patients without external xanthomatosis. The data on families 4 and 11 illustrate that xanthomatosis may occur in a few members or only 1 member of a family, while relatives have heart disease and hypercholesteremia. I have listed also families 15, 16 and 17, in which external xanthomatosis was not demonstrated at all. In favor of xanthomatosis as the cause of heart disease in these three families were the hereditary occurrence and the hypercholesteremia. I wish to mention, too, the postmortem observations in case 64 (family 15), which resembled notably those in case 13 (family 4), in which xanthoma tuberosum was present.

Of great clinical interest is the observation that in xanthomatosis, angina pectoris not only may occur at an early age with sudden death but more often appears as typical angina pectoris, lasting for years in middle-aged as well as in old persons, that is, at the time this disease usually occurs at 60 to 70 years of age and even later. My reports also contain examples of the occurrence of angina at an earlier age; in 16 cases it commenced before the fiftieth year and in 8 of these between the thirty-first and the fortieth year.

Finally, my cases indicate clearly that xanthomatous heart disease is frequent. The case reports have been collected in the course of about one and one-half years and mainly in the course of my own practice. How many of the 68 cases of heart disease were due to xanthomatosis cannot be determined. That all were not due to xanthomatosis is presumably as certain as that many were. It is remarkable the small role which the usual causes of heart disease—rheumatic fever, syphilis and hypertension—appeared to play in these cases. Hypertension, which usually is regarded as a hereditary factor in heart disease, was encountered relatively infrequently and then usually in a mild form. At the same time it is to be noted that the diagnostic value of hypercholesteremia must not be exaggerated, because large or relatively large values are obtained in a number of conditions in spite of the fact that there is no essential xanthomatosis. But this reservation must not be assigned great importance. It should be mentioned that the cholesterol content of the blood in ordinary senile atherosclerosis, according to the recent investigations of Koch and Westphal,[9] as a rule is normal (about 160 mg. per hundred cubic centimeters in 7 of 8 cases, in 1 case being 260 mg.). The hypercholesteremia demonstrated in hypertension is usually moderate and as a rule much lower than was the case in my material. Even if my experiences do not permit any final or definite statements about the frequency of the disease, they do leave the impression that it must be much more frequent than heretofore recognized. The frequency is illustrated by the fact that 1 of my families (family 13) was found by accident because a member (case 59) was married (but not related by blood) to a member of another family (case 19, family 6). The hereditary tendency to xanthomatosis and heart disease appears clearly established in both these families. That such instances have thus far been observed so infrequently may be variously explained. In the first place, the clinicians have not paid attention to the concurrence of the factors and conditions on which the diagnosis depends. Usually xanthelasma is regarded as an insignificant process and perhaps is not even noted in the case records, and both xanthelasma and xanthoma deposits may be so small as readily to escape observation. Determination of the cholesterol content of the blood is not carried out routinely in clinical practice, and in the case of heart disease, heredity is usually regarded as of little importance. The patients in question had no obvious external peculiarities characteristic of their condition; they all looked like ordinary persons. Usually the cardiac symptoms develop at the same age and are of the same kind as those of ordinary angina pectoris. It must be pointed out also that the anatomic changes in the heart and blood vessels are not distinctive and cannot be differentiated

9. Koch, K., and Westphal, K.: Deutsches Arch. f. klin. Med. **181**:413, 1938.

from common arteriosclerosis either grossly or microscopically. That pathogenically and etiologically distinct diseases, especially chronic disease, may lead to the same anatomic changes is illustrated by chronic nephritis and chronic arthritis. The hereditary occurrence of arteriosclerosis in xanthomatosis, the hypercholesteremia and the development of vascular disease early in life, even in children, indicate that a special form of atherosclerosis is concerned which in any case has well marked clinical characteristics. The interesting question as to whether this xanthomatous form of arteriosclerosis can be differentiated anatomically from the senile form has not been discussed to any extent in previous communications. Harbitz,[4b] however, has called attention to certain peculiarities of the xanthomatous form. Microscopically he found that the so-called foam cells are more marked and more characteristic than in senile arteriosclerosis. Macroscopically the deposits are intensely yellow, are more circumscribed, are irregularly distributed and are often in the form of nodes or clumps which may become large enough to obstruct the circulation. In ordinary arteriosclerosis the changes are said to be more diffuse. The changes in my cases 13 and 64 were, however, quite diffuse; in both cases the aorta and its large branches as well as the pulmonary artery were involved. The intimal deposits were markedly yellow. In case 13 there was considerable calcification, which was almost absent in case 34 (figs. 13 and 19). The question of the identity of the arteriosclerosis in xanthomatosis with senile arteriosclerosis requires further study.

It is noteworthy that in xanthomatosis the vascular changes so frequently manifest themselves clinically in coronary disease and angina pectoris. In such a "system disease" one would expect also that other localizations, first of all the cerebral arteries, would cause symptoms. In my series there was only 1 death from apoplexy (case 64, family 15), and this patient had at the same time cardiac infarction. It may be that the coronary arteries do suffer earlier and more than other arteries or that lesions in the coronary arteries give rise more readily to symptoms. In this matter also further investigation is needed.

The treatment of the cardiac symptoms in xanthomatosis differs in no point from the treatment of cardiac symptoms under other conditions. The patients are benefited by quiet, rest in bed and nitrites. Is there a causal therapy? Xanthoma disseminatum diabeticorum may disappear on treatment with insulin and appropriate diet. It has been shown that the cholesterol content of the blood can be reduced by a diet poor in cholesterol. Koch and Westphal[9] obtained the same effect with thyroid preparations. I have ordered a diet poor in cholesterol (no yolk of egg, butter, cream, fat milk or animal fat in general) and thyroid

tablets, but I have not been able to formulate any opinion in regard to the effects. The treatment may be of prophylactic value to persons with a hereditary predisposition.

SUMMARY

Hereditary heart disease due to xanthomatosis is fairly common. It is believed to have been demonstrated as a dominant factor in seventeen families. Xanthomatosis gives rise to a special form of arteriosclerosis which is etiologically and, consequently, clinically different from ordinary arteriosclerosis. It is possible that it may be different anatomically, too. Xanthomatous deposits may cause valvular lesions, but far more commonly the changes are in the coronary arteries, with angina pectoris. This may occur in young but more frequently in middle-aged and old persons. Symptomatically this form of angina pectoris does not differ from the usual form. In addition to chronic and long-continued heart disease, the condition may cause sudden death. Infarction of the myocardium is also a frequent result. Hypercholesteremia is present, most marked in connection with xanthoma tuberosum, but there is no definite relation between hypercholesteremia and xanthomatous deposits in the skin. Xanthomatous cardiac lesions probably may develop in persons who have no evidence of xanthomatosis in the skin. Xanthoma tuberosum and xanthelasma may be overlooked in clinical examinations and may be confused with other cutaneous conditions also. The occurrence of heart disease in families should direct the attention to xanthomatosis, especially when rheumatic fever, syphilis or hypertension does not appear to play any role. In the cases here reported, hypertension was infrequent. Finally, it seems possible that causal and prophylactic treatment may prove to be of value.

CHRONIC LEUKEMIA

THE EARLY PHASE OF CHRONIC LEUKEMIA, THE RESULTS OF TREATMENT AND THE EFFECTS OF COMPLICATING INFECTIONS; A STUDY OF EIGHTY-SIX ADULTS

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The opportunity to observe the course of chronic leukemia from a time before the disease has caused symptoms is necessarily rare, and few accounts of such opportunities are available in the literature. For this reason we have thought it worth while to describe several cases of very early leukemia which we have studied and to review the available information concerning the course of this disease.

An analysis of the cases of chronic leukemia in patients treated at the Johns Hopkins Hospital was also prompted by the frequently made statement that patients suffering from leukemia may, under the influence of infection, exhibit a reversal from a frankly leukemic picture to one closely simulating the blood picture of normal persons and that other manifestations of a remission may appear at the same time. This statement has been repeated so often that the impression is current that it is common for infections to cause a remission in chronic leukemia. Our own experience is quite to the contrary.

Finally, because of the recent renewal of interest in arsenical therapy, a brief account is given of the comparative effectiveness of irradiation and of potassium arsenite in the treatment of leukemia, and the relative responsiveness to therapy of the myelogenous and lymphogenous types of the disease is discussed.

MATERIAL

All cases of chronic leukemia in adults who were observed at this hospital between January 1926 and August 1938, inclusive, are included in this report. Two thirds of the patients were personally studied by one of us (M. M. W.), and full data regarding the others were available in the hospital records. Many of the patients were observed at this hospital continuously or at intervals during their illness, and by correspondence with the patients, their relatives, friends or private physicians, the subsequent course in a number of the other cases was ascertained.

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The diagnosis of leukemia was carefully reconsidered in each instance, and only those cases are included which clearly meet generally recognized diagnostic criteria. The series includes 39 cases of myelogenous and 47 cases of lymphogenous leukemia. Autopsies were made in 28 cases, 14 of each type. Fifteen patients are still alive. Seven of the 39 patients with myelogenous leukemia and 8 of the 47 with lymphogenous leukemia were Negroes.

SEX AND AGE INCIDENCE

Of the patients with myelogenous leukemia, 24 (61.5 per cent) were males. This sex incidence corresponds almost exactly with that in the 605 cases collected from reports in the literature, as well as that in the experience of Minot, Buckman and Isaacs [1] and in the 180 cases reviewed recently by Leavell,[2] in both of which groups the proportion of males was 60 per cent. Of the 82 patients reported on by Hoffman and Craver,[3] 68 per cent were males.

Thirty-nine (83 per cent) of our patients with chronic lymphogenous leukemia were men. The relatively high incidence of this type of leukemia in the male sex is well recognized. Seventy-five per cent of Ward's [4] 84 patients, 74 per cent of the 92 patients reported on by Minot and Isaacs [5] and 72 per cent of Leavell's [2] 128 patients were males.

In agreement with the observations of many writers, the age at onset was earlier in those with myelogenous than in those with lymphogenous leukemia (chart 1). In the total of 675 cases reported by Ward,[4] Minot, Buckman and Isaacs,[1] Hoffman and Craver [3] and Leavell,[2] the age at the onset of symptoms was most frequently between 30 and 50 years, and the decade in which the disease was most common was 35 to 45 years. Rosenthal and Harris [6] have given 30 to 39 years as the decade of greatest incidence. In 30.8 per cent of our patients, symptoms first developed at this age, and in 72 per cent the age at onset was between 30 and 59 years.

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1. Minot, G. R.; Buckman, T. E., and Isaacs, R.: Chronic Myelogenous Leukemia: Age Incidence, Duration, and Benefit Derived from Irradiation, J. A. M. A. **82**:1489 (May 10) 1924.

2. Leavell, B. S.: Chronic Leukemia: A Study of the Incidence and Factors Influencing the Duration of Life, Am. J. M. Sc. **196**:329, 1938.

3. Hoffman, W. J., and Craver, L. F.: Chronic Myelogenous Leukemia: Value of Irradiation and Its Effect on the Duration of Life, J. A. M. A. **97**:836 (Sept. 19) 1931.

4. Ward, G.: The Infection Theory of Acute Leukemia, Brit. J. Child. Dis. **14**:10, 1917.

5. Minot, G. R., and Isaacs, R.: Lymphatic Leukemia: Age Incidence, Duration and Benefit Derived from Irradiation, Boston M. & S. J. **191**:1, 1924.

6. Rosenthal, N., and Harris, W.: Leukemia: Its Diagnosis and Treatment, J. A. M. A. **104**:702 (March 2) 1935.

In the cases of chronic lymphogenous leukemia, on the other hand, the decade in which the disease was encountered most often was 60 to 69 years, and in 61.7 per cent of the cases symptoms began between the ages of 50 and 69 years. Again our data are in somewhat better agreement with those of Rosenthal and Harris,[6] who observed this disease most frequently in patients between the ages of 50 and 69, than with those of Ward,[4] Minot and Isaacs [5] and Leavell,[2] who found the greatest number of cases in patients between the ages of 45 and 54.

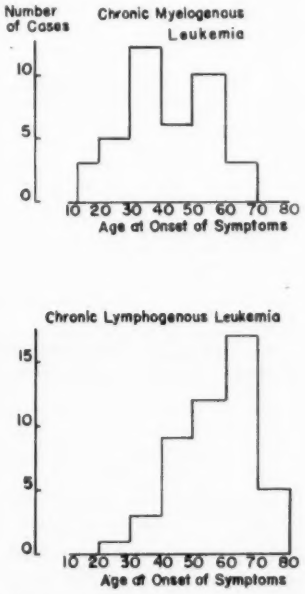

Chart 1.—The age at the onset of symptoms in 39 cases of chronic myelogenous leukemia and in 47 cases of chronic lymphogenous leukemia.

EARLY PHASE OF CHRONIC LEUKEMIA

Because of the insidious character of this disease, it is usually recognized for the first time after widespread anatomic and physiologic abnormalities have developed. As already stated, we have had the opportunity to observe a number of patients from a time when symptoms and signs as well as changes in the blood were minimal or totally lacking until death occurred and autopsy confirmed the diagnosis, or at least until the clinical picture became so characteristic that there was little doubt about the correctness of the diagnosis.

Chronic Myelogenous Leukemia.—In 3 patients who subsequently showed the typical clinical picture of chronic myelogenous leukemia, unexplained leukocytosis was found in the course of routine examinations following pregnancy in 1 case, for sterility in another and because of symptoms suggestive of disease of the gallbladder in the third. All 3 were young adults (28, 29 and 28 years of age, respectively). In the first patient (M. J., chart 2) the spleen was found to extend about 2 cm. below the costal margin, the liver was just palpable and there was slight glandular enlargement in the axillas and groin. However, there was no anemia, and the leukocytes numbered only 28,000, of which 6 per cent were myelocytes and a total of 82 per cent were

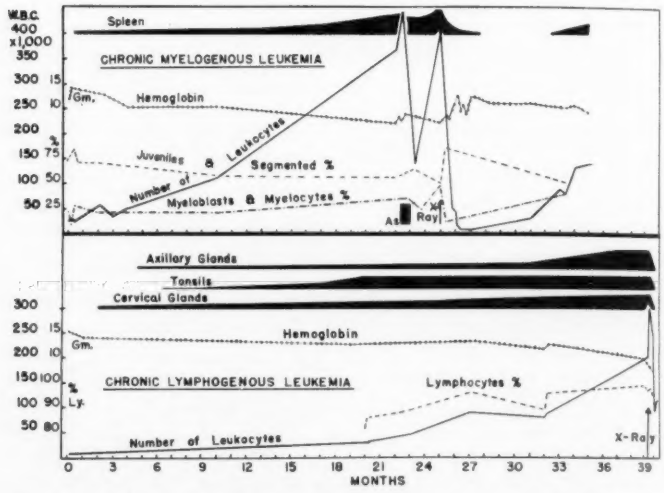

Chart 2.—Diagrammatic presentation of the data in a case (M. J.) of chronic myelogenous leukemia and in a case (H. V.) of chronic lymphogenous leukemia. In each case the disease was discovered early in its course. The initial sign in the case of myelogenous leukemia was unexplained leukocytosis; that in the case of lymphogenous leukemia was glandular enlargement.

As indicates treatment with solution of potassium arsenite U. S. P.; arrows marked "x-ray" indicate when irradiation was given.

myeloid leukocytes. The platelets were very numerous (1,200,000). Slight anemia developed 4 months after the leukocytosis was discovered. Six months later the leukocyte count was 116,800 (myeloblasts, 1 per cent; myelocytes, 24 per cent). It was 22 months after leukocytosis was first discovered before it was thought advisable to give treatment. The leukocyte count at this time was 377,000 and the red blood cell

count 2,590,000, but there were no complaints. This patient is still symptomatically well and able to do her housework, 3 years after the discovery of leukemia.

The second patient (R. H. H.) showed a leukocyte count at the first examination of 77,000 (myeloblasts, 5 per cent; myelocytes, 25 per cent), and there was slight anemia (red blood cells, 4,200,000; hemoglobin, 14.7 Gm.), but physical examination revealed no abnormality except for the presence of a few small lymph nodes in the neck. It was 2.5 years before he sought medical assistance because of weakness and increased fatigability. At that time the leukocytes numbered 337,000, and the red blood cell count was 2,860,000. This man has received roentgen irradiation recently and is still carrying on active executive work without interruption, 4 years after the discovery of the disease.

The patient whose complaints suggested disease of the gallbladder (J. S.) was found to be anemic (hemoglobin, 8.7 Gm.; hypochromic anemia probably due to other causes) and unexplained leukocytosis (26,000 cells) was recorded. Eighty-five per cent of the leukocytes were segmented neutrophils, and 4 per cent were juvenile forms. Physical examination showed no abnormality at this time, and it was not until 3 years and 9 months later that the spleen was palpable. Four years and 2 months later, after delivery of a healthy child, the leukocyte count was found to be 95,800; the spleen, liver and a few lymph nodes were palpable. The red blood cell count was 2,860,000, but this could be attributed chiefly to excessive loss of blood at the time of delivery. The progress of the leukemia in this case has been unusually slow. The patient was recently admitted to the Johns Hopkins Hospital because of an incomplete abortion. At the last examination, 5 years and 4 months after the unexplained leukocytosis was discovered, the liver, spleen and lymph nodes were still only moderately enlarged, the erythrocyte count was 3,090,000 and the leukocytes numbered 92,900. She has had no treatment for leukemia and has carried on her housework except when interrupted by the aforementioned pregnancy and abortion.

A fourth patient (H. R., a man aged 62 years) complained of abdominal distress. There was no anemia, but the leukocytes numbered 20,000. It was not until 1 year later that the spleen and liver were palpable, the leukocytes numbered 80,000, with 5 per cent myeloblasts as well as 25 per cent myelocytes, and there was slight anemia (red blood cells, 4,100,000; hemoglobin, 13 Gm.). Another patient (C. M., a woman aged 34 years) came under observation because of uterine myomas and was found to have a slightly enlarged spleen but scarcely any leukocytosis (11,000 cells, of which 76 per cent were polymorphonuclear neutrophils). It was 3 years before the spleen was

greatly enlarged. The leukocyte count had increased to only 40,000 (1.5 per cent myeloblasts, 18 per cent myelocytes and 91 per cent total myeloid leukocytes, with no anemia).

In these 5 cases in which chronic myelogenous leukemia was discovered at a presumably very early stage, it is noteworthy that unexplained leukocytosis (11,000 to 77,000 cells) was the first sign of the disease. In 2 cases physical examination revealed no abnormality. Another patient, whose leukocyte count was as high as 77,000, had slight anemia, and only a few glands were palpable in the angles of the mandible on careful examination. This was the only instance among the 5 cases in which anemia attributable to the leukemic process was found. In the cases in which the leukocyte counts were low, myelocytes, which are so characteristic of the blood picture in the fully developed stage of this disease, were absent or few, and the leukocytosis was chiefly due to an increase in the number of segmented forms.

It is difficult to estimate how long a time would have elapsed before these patients would have sought medical aid on account of symptoms attributable to leukemia. One of these patients was lost sight of after the initial examination, at which a leukocyte count of 77,000 was found. He returned of his own accord because of weakness, 2.5 years later. A reasonable estimate of the time elapsing from the onset of chronic myelogenous leukemia until symptoms of the disease commonly cause the patient to seek medical attention is probably 2 to 5 years or longer.

Chronic Lymphogenous Leukemia.—Data concerning the early phase of chronic lymphogenous leukemia were available in 16 cases. This disease was first discovered in 3 patients when they presented themselves because of symptoms due to prostatic hypertrophy. These men were 59, 67 and 72 years of age, respectively. In H. V. (chart 2) the only finding suggesting disease other than prostatic hypertrophy was enlargement of the tonsils and of a few lymph nodes in the axillas. Neither the spleen nor the liver was enlarged, there was no anemia and the leukocyte count was 8,500. After prostatectomy, glandular enlargement developed slowly, and after 1.5 years the leukocyte count was 29,000, with 83 per cent lymphocytes. It was 2.3 years before the liver became palpable, and not until more than 3 years after glandular enlargement was first discovered was there the clinical picture usually associated with lymphogenous leukemia (great enlargement of the lymph nodes and tonsils, 204,000 leukocytes, 3,140,000 red blood cells and a hemoglobin value of 10.1 Gm.). Treatment was instituted shortly afterward, but the patient died 3 months later of bronchopneumonia.

The history of W. A. G. differed from the foregoing in that the first evidence of lymphogenous leukemia was leukocytosis (52,500 cells,

with 97 per cent lymphocytes) with moderate anemia (red blood cells, 3,600,000; hemoglobin, 10.1 Gm.) rather than glandular enlargement. This patient died 4.5 years later of pneumonia. In the third case (F. S.) slight glandular enlargement, splenomegaly and moderate leukocytosis (37,300 cells, with 88 per cent lymphocytes) without anemia were the initial findings.

Routine examination, undertaken because sugar had been found in the urine, revealed slight cervical and inguinal glandular enlargement, leukocytosis (34,000 cells, with 86 per cent lymphocytes) and no anemia in a man of 63 years (A. E. S.). This patient died 5 years later. A psychoneurotic disorder brought E. S. (a woman aged 61 years) under observation. Enlargement of the tonsils, a palpable liver and spleen, and leukocytosis (61,400 cells, with 82 per cent lymphocytes) without anemia were the findings of interest. R. P. E., a man aged 73 years, was seen because of "indigestion." There was slight glandular, splenic and hepatic enlargement, the leukocytes numbered 16,800, with 60 per cent lymphocytes, and there was no anemia. He died 2 years later of bronchopneumonia.

Unlike the cases of myelogenous leukemia, the finding of unexplained leukocytosis was the first evidence of the disease in only about a third of the cases of early lymphogenous leukemia. In another third of the cases, glandular enlargement was the sign which first attracted attention. Four patients observed this themselves. By the time they were examined the leukocyte count in 3 instances was still relatively low (19,900, 20,000 and 32,600, respectively, with 73 to 90 per cent lymphocytes). In only 1 case (M. S.) was splenic enlargement the most prominent early sign. The spleen was so large and the blood findings were so normal (leukocytes, 9,000, with lymphocytes, 29 per cent) that splenectomy was performed, the impression being that this was an example of Banti's disease. Subsequently the leukocyte count gradually rose, and when the patient was first seen by one of us, 2 years later, the leukocyte count was 121,000, the lymphocytes numbered 76 per cent and slight glandular enlargement and marked enlargement of the liver were noted. There was no anemia.

It is noteworthy that lymphocytosis was present in a number of cases even when the leukocyte count was still relatively low. Thus in 2 cases in which the leukocyte count was 13,000 and 16,800, respectively, 60 per cent of these cells were lymphocytes; in 2 cases, in which the leukocytes numbered 28,000 and 29,000, respectively, the proportion of lymphocytes was 74 and 83 per cent, respectively; in 3 cases, in which the leukocytes numbered 32,600, 34,000 and 37,000, respectively, the percentage of lymphocytes was 90, 86 and 88, respectively. The early rise

in the proportion of lymphocytes was first noted by Ortner,[7] and its diagnostic significance was emphasized by Pinkus,[8] by whose name this sign is sometimes known.

Comment.—Whereas anemia was not found in the cases of myelogenous leukemia in the very early stages, in several of the cases of lymphogenous leukemia slight anemia was present at what otherwise appeared to be an early stage of the disease.

The time interval between the finding of signs which aroused suspicion of the presence of lymphogenous leukemia and the development of symptoms of the disease, as judged by the records in our cases, was about 1.5 to 2.5 years. The earlier recognition of lymphogenous leukemia, as compared with that of myelogenous leukemia, in our series is explained by the greater frequency with which glandular enlargement sufficient to attract attention occurred in the patients with lymphogenous leukemia.

THERAPEUTIC RESULTS

The results of treatment in cases in which there are adequate data are summarized in table 1. These data are limited to the effects of the first course of treatment, because in patients subjected to many courses of treatment, it is known that sooner or later the response becomes less satisfactory. In the table no distinction is made between the effects of radium and of roentgen rays. Solution of potassium arsenite U. S. P. (Fowler's solution) was given in the manner recommended by Forkner.[9] All but 1 of the patients with myelogenous leukemia who were given this solution subsequently received irradiation; this is also true of 2 of the 5 patients with lymphogenous leukemia given this solution. Table 1 therefore gives the results of treatment in a total of 30 cases of myelogenous leukemia and 25 cases of lymphogenous leukemia.

Potassium arsenite proved to be of no value in a small group of cases of lymphogenous leukemia, and in the cases of myelogenous leukemia the results of treatment with this drug were less satisfactory than those following irradiation. We have found toxic symptoms following the use of potassium arsenite more troublesome than those associated with irradiation, and the effect on the blood has been more temporary than that produced by roentgen irradiation.

The response to irradiation was slightly better in the cases of myelogenous leukemia than in the cases of lymphogenous leukemia. In

7. Ortner, N.: Leukämie und Pseudoleukämie, Wien. klin. Wchnschr. **3**:677, 1890.

8. Pinkus, F.: Die lymphatische Leukämie, in Nothnagel, H.: Specielle Pathologie und Therapie, Vienna, A. Hölder, 1897, p. 90.

9. Forkner, C. E.: The Administration of Solution of Potassium Arsenite in the Treatment of Chronic Myelogenous Leukemia, M. Clin. North America **15**: 1057, 1932.

the tabulated data this is indicated chiefly by the greater frequency with which anemia decreased under treatment in the former group of patients than in the latter.

TABLE 1.—*Results of First Courses of Treatment in Thirty Cases of Chronic Myelogenous Leukemia and Twenty-Five Cases of Chronic Lymphogenous Leukemia*

	Myelogenous		Lymphogenous	
	Irradiation	Solution of Potassium Arsenite U.S.P.	Irradiation	Solution of Potassium Arsenite U.S.P.
Total number of cases	29	8	22	5
Leukocytes:				
Decreased	29	6	19	0
Unchanged	0	1	3*	4
Increased	0	1†	0	1
Anemia:				
Decreased	13	0	2	0
Unchanged	8	6	17	2
Increased	4	2	1	3
No data	4	0	2	0
Clinical status (objective):				
Improved	27	1	20	0
Unchanged	2‡	5	2	3
Worse	0	2	0	2
Clinical status (subjective):				
Improved	28	1	19	0
Unchanged	1	5	3	3
Worse	0	2	0	2

* In 1 of these cases treatment was probably inadequate. In the 2 other cases the leukocyte count was normal when treatment was commenced; in neither case did the red blood cell count rise after roentgen treatment, but the clinical status improved.
† Possibly due to inadequate dosage.
‡ In 1 of these cases the unchanged objective clinical status might have been due to insufficient treatment.

TABLE 2.—*Data on Time Intervals*

	Chronic Myelogenous Leukemia		Chronic Lymphogenous Leukemia	
	Time, Years	No. of Cases	Time, Years	No. of Cases
Time elapsing between onset of symptoms and recognition of disease	1.11	36	1.26	35
Length of life after diagnosis was made	1.68	23	1.07	23
Total time from recognition of disease to death	2.79		2.33	

These results are essentially in agreement with those recorded in the literature.[10]

10. (*a*) Forkner, C. E.: Leukemia and Allied Disorders, New York, The Macmillan Company, 1938, p. 52. (*b*) Minot, Buckman and Isaacs.[1] Hoffman and Craver.[3] Minot and Isaacs.[5] Rosenthal and Harris.[6]

DURATION OF LIFE

The average time elapsing between the onset of symptoms and the recognition of leukemia in all our cases, including the cases in which the patients were seen very early in the course, is shown in table 2. The time interval is somewhat shorter than that (1.4 years) recorded by Minot and his co-workers.[11] The length of life after the diagnosis was made and the time elapsing between the onset of symptoms and death were shorter than other investigators have found them to be. The average duration of life in the 236 cases of chronic myelogenous leukemia reported by Minot, Buckman and Isaacs,[1] Hoffman and Craver [3] and Leavell [2] was 3.34 years, and the duration in 129 cases of chronic lymphogenous leukemia reported by Minot and Isaacs [5] and Leavell [2] was 3.52 years.

There is great variation in the duration of life in cases of chronic leukemia. The natural course of the disease may be extremely slow. A case of lymphogenous leukemia of 25 years' duration was recently described.[12] As many as 14 per cent of the patients treated by Minot and Isaacs [5] lived 6 to 8 years. Of their patients with myelogenous leukemia,[1] 12 per cent lived 5 to 10 years. Four of the patients with myelogenous leukemia reported by Hoffman and Craver [3] lived 16.5, 16, 12.5 and 11 years, respectively. The duration of the disease in these cases must actually have been longer, because in most instances the data referred to duration from the time of the onset of symptoms.

In other cases the disease progresses rapidly, some conditions being encountered in which it is difficult to classify the process as belonging in either of the artificial categories of acute and chronic which custom has set up. In addition, intercurrent infection, cardiac failure or some other disorder not infrequently terminates the course in cases of otherwise slowly progressive leukemia.

INCIDENCE OF INFECTIONS IN CHRONIC MYELOGENOUS AND LYMPHOGENOUS LEUKEMIA; EFFECTS ON LEUKOCYTE COUNT AND CLINICAL STATUS

It is frequently stated that patients presenting the classic clinical and hematologic picture of leukemia often exhibit in the presence of infection a marked decrease in the leukocyte count; even the organs enlarged by the leukemic disorder may decrease in size. This statement has been repeated in textbooks and is found in Forkner's [10a] recent monograph as well as in Downey's handbook.[13] It arises from observa-

11. Minot, Buckman and Isaacs.[1] Minot and Isaacs.[5]

12. McGavran, C. W.: Lymphatic Leukemia of Twenty-Five Years' Duration, Ann. Int. Med. **12**:396, 1938.

13. Richter, M. N.: Leucemia, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 4, p. 2992.

tions made toward the end of the last century. Dock [14] reviewed the evidence in 1904 and cited several cases of his own.

If this paradox is correct, it is truly a remarkable phenomenon and is of great interest in view of the conception that leukemia is related to malignant tumors. All our cases have been carefully reviewed with the object of noting the incidence of infections and the reaction accompanying these infections. The data are recorded in tables 3 to 5. In tables 4 and 5 the leukocyte counts found at about the time of the highest elevation of temperature are given. Except for syphilis, dental caries and asymptomatic infections like those indicated by chronically infected tonsils, all types of infection encountered in our cases are included.

It is of interest that, although the series consists of 39 cases of myelogenous and 47 of lymphogenous leukemia, there were only 11

TABLE 3.—*Pyogenic and Tuberculous Infections in Cases of Chronic Leukemia* *

	Myelogenous	Lymphogenous
Acute tonsillitis or peritonsillar abscess	2	0
Otitis media, abscess of brain and acute meningitis	0	1
Chronic sinusitis	0	1
Furunculosis	0	2
Influenza	0	3
Lobar pneumonia (pneumococcus)	0	7
Bronchopneumonia	2	4
Chronic bronchitis	1	0
Bronchiectasis	0	2
Acute infections involving the genitourinary tract	2	4
Subacute or chronic infections involving the genitourinary tract	2	2
Gonorrheal arthritis and bacteremia	1	0
Acute enteritis (Flexner's bacillus)	0	1
Peritonitis (pneumococcus)	0	1
Perirectal abscess	1	0
Acute mastitis and septicemia (beta hemolytic streptococcus) with widespread extrapulmonary tuberculosis	1	0
Total number of infections	12	28

* There were 11 cases of myelogenous and 18 of lymphogenous leukemia.

cases of infection (28.2 per cent) in the former group, whereas 18 (38.2 per cent) occurred in the latter. It was common, moreover, to find more than one type of infection in the cases of lymphogenous leukemia (table 3). The higher incidence of infection in the cases of lymphogenous leukemia is also indicated by a review of the autopsy records. In 28 (14 of each type) of our series of 86 cases an examination was made in the department of pathology. Anatomic evidence of pyogenic infection was found in 5 cases of chronic myelogenous leukemia and in 10 cases of the lymphogenous type.

A striking difference in the two groups was the occurrence of 7 instances of lobar pneumonia in the cases of lymphogenous leukemia and the absence of this type of infection in the cases of myelogenous

14. Dock, G.: The Influence of Complicating Diseases upon Leukaemia, Am. J. M. Sc. **127**:563, 1904.

leukemia. With 1 exception the outcome was fatal. This patient was the only one not observed during the course of the infection at this hospital, but the diagnosis was corroborated by a report from the hospital where he remained during the attack of pneumonia.

Clinical improvement in the leukemic signs or a quantitative or qualitative change in the blood in the direction of normal was observed in only 1 case of early chronic lymphogenous leukemia (A. E. S.). This patient's leukemia was accidentally discovered in a routine exam-

TABLE 4.—*Leukocytic Picture During Infections in Cases of Chronic Myelogenous Leukemia*

				Differential Counts, %								
Patient	Infection	Maximum Temperature, F.	Leukocytes, Total Count	Myeloblasts	Myelocytes	Juvenile Neutrophils	Segmented Neutrophils	Eosinophils	Basophils	Lymphocytes	Monocytes	End Result
A. K.	Acute tonsillitis....	101.8	90,000	1	42	30	25	0.4	0.3	1.0	0.3	Recovered
E. P.	Acute peritonsillar abscess	100.8	241,000	1	14	16	66	1.0	0	2.0	0	Recovered
J. S. H.	Bronchopneumonia	103.6	490,000	13	62	0	23	0	0	0	0	Died
S. S.	Bronchopneumonia	104.4	5,500*	0	7	0	87	0	1.0	0	5.0	Died†
A. G.	Chronic bronchitis.	101.0	80,000	10	37	..	46	7.0	0	0	0	Unchanged
H. V. K.	Pyelonephritis.....	105.4	82,000	6	37	30	26	0	0	1.0	0	Died‡
R. B.	Chronic cystitis, prostatitis and urethritis	99.4	34,000	6	58	18	8	0	0	0	0	Died‡
C. W.	Gonococcic arthritis and septicemia	104.4	156,000	2	19	2	70	0	0	4.0	1.0	Recovered
W. H. R.	Gonococcic urethritis (subacute)	100.2	48,700*	0	4	25	65	1.0	3.0	1.0	1.0	Recovered
A. G.	Acute mastitis and septicemia (beta hemolytic streptococcus) and extrapulmonary tuberculosis	103.0	327,000	0	22	16	53	5.0	2.0	2.0	0	Died†
M. N.	Perirectal abscess (Bacillus coli)	104.0	21,000*	0.5	9	20	62	0	1.0	7.5	0	Recovered

* In this case the low leukocyte count was the result of roentgen treatment.
† In this case the diagnosis was confirmed by autopsy.
‡ Death was not due to the infection.

ination. There was no anemia, but moderate general glandular enlargement as well as leukocytosis (34,000 cells, with 94 per cent lymphocytes) was found. The development of an infection of the respiratory tract was accompanied by a slight decrease in the total leukocyte count (to 23,400) on the day when the fever was most marked (102.6 F.). At the same time the proportion of lymphocytes decreased to 59 per cent, the absolute number of polymorphonuclear leukocytes thus having increased from about 2,000 to a maximum of 9,600 per cubic millimeter. Two weeks later, when the fever had subsided, the leukocyte count was 32,000, with 69 per cent lymphocytes. A moderate increase in the size of the lymph nodes occurred during the infection of the respiratory tract.

In the majority of the cases the blood picture remained essentially unchanged when infection developed. In 4 cases of lymphogenous leukemia (table 5; C. G., R. K., C. F. and I. M.) an increase in the number of leukocytes actually occurred.

On entry because of prostatic disease, the leukocyte count of C. G. was 14,920 per cubic millimeter, with 45 per cent lymphocytes. Extrav-

TABLE 5.—*Leukocytic Picture During Infections in Cases of Chronic Lymphogenous Leukemia*

				Differential Counts, %					
Patient	Infection	Maximum Temperature, F.	Leukocytes, Total Count	Juvenile Neutrophils	Segmented Neutrophils	Eosinophils	Lymphocytes	Monocytes	End Result
R. K.	Otitis media; abscess of the brain; acute meningitis	103.0	27,400	0	8	0	91	1	Died*
M. B.	Chronic purulent pansinusitis; bronchiectasis	101.0	51,200	0	10	0	90	0	Unchanged
J. K.	Influenza	102.8	57,600	0	4	0.5	95	0.5	Recovered
J. W. S.	Influenza	103.6	84,000	..	..	..	..	..	Recovered
A. E. S.	Influenza	102.6	23,400	0	41	0	59	0	Recovered
C. G.	Urinary extravasation; abscess in space of Retzius; lobar pneumonia	103.0 104.6	41,600 16,750	0 0	21 67	0 1.0	79 32	0 0	Died*
K. R.	Lobar pneumonia	103.4	122,500	0	30	0	69	1.0	Died*
M. C.	Lobar pneumonia; acute meningitis; septicemia	104.8	72,000	1	1	0	98	0	Died*
M. R.	Lobar pneumonia; peritonitis	101.8	19,300†	0	45	1	54	0	Died*
C. F.	Lobar pneumonia; chronic cystitis (B. coli)	104.0	204,800	0	5	0	95	0	Died*
W. W.	Lobar pneumonia	103.9	5,200	0	62	0	36	0	Died*
E. J. L.	Lobar pneumonia; cystitis (B. coli); acute pyelitis	..... 103.6	95,000 45,000	0 2	15 29	0 0.5	85 68.5	0 0	Recovered Unchanged
L. B.	Bronchopneumonia	102.8	30,000	0	5	0	93	2	Died*
R. P. E.	Bronchopneumonia	104.0	36,600	0	51	0	48	1	Died
H. V.	Bronchopneumonia	103.0	110,000	0	2	0	98	0	Died
I. M.	Bronchopneumonia; acute cystitis	105.0	120,000	0	0.5	0	99.5	0	Died*
F. S.	Acute epididymitis	104.0	68,400	6	24	1	66	3	Recovered
R. L.	Acute enteritis	103.0	71,000	0	1	0	99	0	Died*

* In this case the diagnosis was confirmed by autopsy.
† In this case the low leukocyte count was the result of roentgen treatment.

asation of urine and the development of an abscess in the space of Retzius was accompanied by fever (102 to 104.6 F.) and an increase in the number of leukocytes to a maximum of 65,300 (77 per cent lymphocytes) on the fifth day of fever. On subsidence of temperature to a level of 102 to 100 F. following suprapubic cystotomy and drainage of the lateral and prevesical spaces, the leukocyte count gradually dropped to 20,000 (48 per cent lymphocytes). A month after the operation and 12 days after these blood findings were noted, the temperature increased to 104.6 F., and the leukocyte count was found to

be 16,750, with 32 per cent lymphocytes. This, it will be noted, was similar to the blood picture on entry. The patient died the next day, and at autopsy lobar pneumonia, abscesses in the prostate and right testicle, and the typical changes of chronic lymphogenous leukemia were present.

The leukocyte count of R. K. was 17,440 per cubic millimeter, with 60 per cent lymphocytes, on entry. Transfusion was followed by a decrease to 8,500, with 70 per cent lymphocytes. With the development of otitis media the number of white blood corpuscles increased to 27,400, of which 91 per cent were lymphocytes; in spite of irradiation of the glands of the neck and axillas, the count increased to 56,650, with 90 per cent lymphocytes. The number of leukocytes fluctuated between this level and 28,250 until death occurred, 2 weeks after infection set in. In patient C. F. the development of lobar pneumonia was accompanied by an increase in the number of leukocytes from 103,250, with 97 per cent lymphocytes, to 204,800, with 95 per cent lymphocytes. In patient I. M. the development of bronchopneumonia was associated with fluctuation in the leukocyte count between a minimum of 96,000 and a maximum of 200,000.

It is noteworthy that in patient C. G. the increase in the number of lymphocytes, when an abscess developed in the space of Retzius, was accompanied by an increase in the absolute number of myeloid leukocytes from 8,100 to 15,020 per cubic millimeter. The subsequent attack of lobar pneumonia in this case was accompanied by a rise from 9,800 to only 11,390 leukocytes, even though at this time the ratio of the various types of leukocytes was more normal than it had been previously. In patient C. F. the absolute increase in the number of myeloid leukocytes when pneumonia developed was from a level of about 3,100 to 10,240. In patients R. K. and I. M. the absolute number of polymorphonuclear leukocytes changed very little or actually decreased when infection developed.

Our own experience, then, is not in agreement with the statement which has been repeated so frequently in the medical literature. It is curious that there seems to have been no thought of questioning the view that it is common for a remission to occur in cases of leukemia when an intercurrent infection arises. Actually, Dock's [14] study is not beyond criticism. His first patient, who returned for observation 34 days after the diagnosis of chronic myelogenous leukemia was originally made, stated that 2 weeks before she had had influenza. The leukocyte count, which had been 367,070, was 7,500. However, in citing this case it seems to have been overlooked that this patient had been taking potassium arsenite since the diagnosis of leukemia was first made and that she had taken a large amount is indicated by the fact that she com-

plained of numbness and of pruritus. Dock's second patient was also treated with this drug. This patient disappeared from observation, and the evidence offered regarding the influence of infection consists in the finding at autopsy, 1 year later, of severe tuberculosis of the serous membranes and no leukemic changes in the tissues except in the bone marrow. It is stated that there was no leukocytosis at this time, but apparently no leukocyte count was made before death. In Dock's third case, no decrease in the leukocyte count occurred.

Dock cited 6 cases recorded in the literature in which a marked decrease in the leukocyte count occurred in association with acute tuberculosis and 11 other cases in which such a decrease took place in association with other infections. We have been able to examine the original reports of all but 5 of these cases. In 3 cases adequate leukocyte counts were not made, 2 were cases of atypical leukemia and 2 were cases of acute leukemia which may have passed into an "aleukemic" phase. In most of the reports the treatment was not mentioned, but, as Dock himself pointed out, many of the patients whose cases he cited were taking arsenic, sometimes in large doses. Dock's view that the changes in the leukocyte count could not be ascribed wholly or in part to the drug remains a matter of opinion. It is now well recognized that a remission will occur in chronic myelogenous leukemia if large enough doses of potassium arsenite are given.

In 1903 Neutra [15] described a case of chronic lymphogenous leukemia in which the development of lobar pneumonia was accompanied by a striking decrease in the leukocyte count and a diminution in the size of the spleen. He accepted reports of 19 cases recorded in the literature as representing remission in leukemic signs as the result of intercurrent infection but failed to consider the possible effects of arsenical therapy. In the same year Hart [16] recorded a case of chronic lymphogenous leukemia in which the leukocyte count decreased from 1,168,000 to 540,000 when pneumonia developed. Körmöczi [17] described a decrease from 80,000 to 30,000 leukocytes per cubic millimeter accompanying erysipelas in a case of lymphogenous leukemia. Macfie [18] noted a temporary decrease in the leukocyte count in a case of chronic lymphogenous leukemia and in 1 case of the myelogenous type during malarial

15. Neutra, W.: Ueber den Einfluss akuter Infektionskrankheiten auf die Leukämie, Ztschr. f. Heilk. **24**:349, 1903.

16. Hart, S.: Chronic Lymphatic Leukemia Complicated by Pneumonia, New York M. J. **78**:224, 1903.

17. Körmöczi, E.: Ein Fall der lymphatischen Leukämie günstig beeinflusst durch Erysipel, Folia haemat. **11**:297, 1911.

18. Macfie, J. W. S.: An Observation on the Effect of Malaria in Leukaemia, Ann. Trop. Med. **13**:347, 1920.

infection; and Gamble,[19] who attempted to treat patients with leukemia by the inoculation of malaria, observed a prompt fall in the leukocyte count to less than half the previous count in 2 cases, 1 of each type. After the termination of the paroxysms with quinine, the white blood cell count rose, in 6 and 3 days, respectively, to approximately the previous level.

Few reports on this subject have appeared in recent years. In the case reported by Hickling and Sutliff,[20] lobar pneumonia was accompanied by an increase in the leukocyte count from a level of 40,000, with 60 per cent lymphocytes, to 94,000 on the eighth day of the disease. The increase in the total leukocyte count was due chiefly to an increase in lymphocytes, but an absolute increase in polymorphonuclear leukocytes, from 15,000 to 25,000, also occurred. The case reported by MacMahon and Parker,[21] in which a decrease in the leukocyte count occurred in association with septicemia, cannot be regarded as a case of typical chronic leukemia. Veyssi [22] gave a brief account of a case of chronic myelogenous leukemia in which a temporary remission occurred during an acute suppurative process. In the cases of myelogenous leukemia reported by Jaffé [23] and by Gosau,[24] roentgen irradiation may have been responsible for the fall in the leukocyte count. In the case reported by Ryan and Medlar,[25] no marked effect on the leukocyte count was noted.

A critical review indicates, then, that there is little evidence even in the literature to support the thesis that a remission of the leukemic signs frequently occurs in association with an intercurrent infection. In personal communications, two competent observers have informed us that they recall having seen patients with leukemia in whom a temporary remission occurred during the course of an infection, but several other hematologists of considerable experience have not observed such cases. The occurrence of a remission in association with infection in chronic leukemia, particularly in the lymphogenous type, cannot be denied.

19. Gamble, C. J.: Failure of Therapeutic Malaria in the Treatment of Leukemia, J. A. M. A. **88**:87 (Jan. 8) 1927.

20. Hickling, R. A., and Sutliff, W. D.: Pneumonia in a Case of Chronic Lymphatic Leukemia, Am. J. M. Sc. **175**:224, 1928.

21. MacMahon, H. E., and Parker, F., Jr.: A Case of Lymphoblastoma, Hodgkin's Disease and Tuberculosis, Am. J. Path. **6**:367, 1930.

22. Veyssi: Sur un cas de leucémie myéloïde passagèrement améliorée par une infection intercurrente, Soc. de méd. mil. franç., Bull. mens. **28**:187, 1934; abstracted, Am. J. Cancer **26**:876, 1936.

23. Jaffé, R. H.: Tuberculosis and Leukaemia, Am. Rev. Tuberc. **27**:32, 1933.

24. Gosau, J.: Chronische myeloische Leukämie mit Sepsis tuberculosa acutissima, Folia haemat. **52**:271, 1934.

25. Ryan, W. J., and Medlar, E. M.: Coexistence of Lymphocytic Leukemia and Far-Advanced Pulmonary Tuberculosis, Am. Rev. Tuberc. **36**:212, 1937.

However, a remission is probably a very unusual event rather than a common one. It is noteworthy that ours seems to be the first series of consecutive cases which have been analyzed in regard to the effect of infection on the leukemic picture. The reports in the literature deal with only 1 or 2 cases each and probably have given an erroneous impression of the frequency of remissions caused by infections.

It is of interest that in several of our cases of lymphogenous leukemia, the development of infection was accompanied by an increase, rather than a decrease, in lymphocytes and that in a few instances an absolute increase in granulocytes occurred as well. As already mentioned, Hickling and Sutliff [20] noted a similar change. In their case protective antibodies developed in the blood in moderate amount, but no agglutinins were found.

The significance of the increase in the number of lymphocytes is a matter for speculation. The increase in the number of granulocytes probably depends on the persistence of sufficient myeloid tissue to produce mature granulocytes, as Jaffé [26] concluded from his study of the inflammatory defense reactions in 10 cases of leukemia. He was unable to confirm the statements of Bickhardt [27] and others that leukemic cells may take the place of mature granulocytes; he found that in the absence of myeloid tissue the changes in the tissues in response to infection were similar to those seen in granulocytopenia and in aplastic anemia. If this view is correct, it is easy to see why patients with lymphogenous leukemia are particularly vulnerable to infection, as our data suggest.

SUMMARY

A study has been made of 86 patients with chronic leukemia (39 of myelogenous and 47 of lymphogenous leukemia) treated at the Johns Hopkins Hospital.

Males predominated in both groups, 61.5 per cent of the patients with myelogenous leukemia and 83 per cent of the patients with lymphogenous leukemia being males.

In 72 per cent of the cases of myelogenous leukemia the age at onset was 30 to 59 years, while in 61.7 per cent of the cases of lymphogenous leukemia, symptoms began between 50 and 69 years.

The early phase of chronic leukemia, as determined by the histories of 5 patients with myelogenous leukemia and 16 with lymphogenous leukemia, is described.

26. Jaffé, R. H.: Morphology of the Inflammatory Defense Reactions in Leukemia, Arch. Path. **14**:177 (Aug.) 1932.

27. Bickhardt, K.: Ueber morphologische Befunde bei Entzündungsvorgängen in Fällen von Leukämie, Folia haemat. **32**:83, 1925.

These observations indicate that unexplained leukocytosis may be the first and even the only sign of chronic myelogenous leukemia. In these cases mature cells of the myeloid series rather than myelocytes made up the majority of the leukocytes.

In chronic lymphogenous leukemia, unexplained leukocytosis was the initial sign in only about a third of the cases. Slight glandular enlargement was a frequent early sign. In 1 case splenomegaly was so pronounced and other signs were so minimal that an erroneous diagnosis of Banti's syndrome had been made.

Distinct lymphocytosis was found in a number of cases of early lymphogenous leukemia even when the leukocyte count was relatively low.

Slight anemia was found more often in the early stages of lymphogenous leukemia than in those of myelogenous leukemia.

It is estimated that the time elapsing from the onset of chronic myelogenous leukemia until symptoms of the disease commonly cause the patient to seek medical attention is about 2 to 5 years, whereas this period in cases of lymphogenous leukemia may be only about 1.5 to 2.5 years.

Treatment with solution of potassium arsenite U. S. P. was found to be of no value in lymphogenous leukemia and of less value than irradiation in myelogenous leukemia. The response to irradiation was slightly better in myelogenous leukemia.

Statistics concerning the duration of life in cases of chronic leukemia are recorded. It is pointed out that extreme variation occurs in the natural course of the disease in different cases.

Infections were more common in cases of lymphogenous leukemia than in those of myelogenous leukemia.

Contrary to the opinion frequently expressed, infections in the great majority of the cases did not produce a remission in the physical signs or in the blood picture. In only 1 instance did a slight change of this nature occur, and in 4 cases there was an actual increase in the leukocyte count in association with infection.

TRAUMATIC RUPTURE OF THE PERICARDIUM

STUDY OF TWENTY-TWO CASES, WITH TWO AND ONE-HALF YEAR PERIOD OF SURVIVAL IN ONE CASE; REVIEW OF LITERATURE

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The literature on traumatic rupture of the pericardium appears never to have been fully assembled and summarized. As recently as 1928, Spitzmüller [1] made mention of only 3 cases in addition to his own. One might infer therefore that this type of injury is a rarity. However, that such an inference is not correct is readily shown by the fact that in 4,107 necropsies performed by the members of the staff of the department of pathology of the University of Oregon Medical School Hospitals and for the coroner of Multnomah County, Ore., over the eight year period between 1929 and 1937, 22 instances of this nature were encountered, none of which had been previously recorded. In all probability other autopsy statistics, particularly if any considerable number of accidental or violent deaths were investigated, would equal or even exceed this figure. Very probably the paucity of information concerning pericardial rupture is due to the fact that it is so commonly but one of multiple injuries terminating fatally and in itself may or may not contribute to the cause of death.

Our interest in the matter was stimulated by the discovery of an extensive pericardial rent, occurring in the absence of evidence of serious damage to the thoracic or abdominal viscera, in a boy who lived for two and one-half years after an accident with but few symptoms attributable to the lesion present at necropsy. In searching the literature a number of reports were found, some of which appeared to have been overlooked by others. Furthermore, we were struck by the inadequacy of certain of the concepts of the mechanism of production of pericardial rupture. For these reasons and because of the interesting problems of cardiodynamics that may have been present in our case, it appeared that another paper on traumatic defects of the pericardium would be timely.

From the Department of Pathology, the University of Oregon Medical School.

1. Spitzmüller, W.: Ein seltener Fall von Herzbeuteverletzung, Arch. f. klin. Chir. **150**:551, 1928.

REPORT OF CASES

Only the example mentioned in the preceding paragraph demands detailed consideration; the pertinent data of the others are listed in the accompanying table.

J. F., a 7 year old boy, entered St. Vincent's Hospital on July 27, 1934, for tonsillectomy. On this occasion the physical examination disclosed nothing abnormal in the cardiovascular system. Two weeks later he was again admitted to the hospital, one hour after having been run over by a loaded automobile trailer, one wheel of which passed across the upper part of his chest. His sole complaint was of severe pain over the injured area. He was conscious but evidenced some degree of shock. The past history offered nothing suggestive of cardiac or circulatory incompetence.

The blood pressure at this time was 90 systolic and 60 diastolic; the pulse rate was 105 per minute, the respiratory rate 25 and the temperature 98.6 F. Roentgenograms of the thorax and left shoulder were immediately made and disclosed a fracture at the juncture of the middle and the outer third of the clavicle and bilateral thickening of the hilar shadows, with dense peribronchial extensions into the lower lobe of the left lung, but no fractured ribs. However, on physical examination there was noted a distinct deformity over the left third, fourth and fifth ribs, with over-riding fractures of the costochondral junctions of the third and fourth ribs. The leukocyte count at this time was 22,500 with 9 per cent staff cells among the granulocytes. The urine was normal.

After a few hours the temperature became elevated and fluctuated between 98.4 and 100 F. for the next four days, returning to normal on the fifth day, when he was discharged. Clinically, the fever and roentgenographic changes in the thorax were interpreted as due to bronchopneumonia. Tuberculosis was suggested as a possibility but was not considered further. With the return of the temperature to normal, the leukocytosis subsided. During the first two days in the hospital the child complained of pain in the chest, but records made no mention of it afterward. At no time were there symptoms or signs of internal hemorrhage. A second roentgenogram of the chest, made on the day of discharge, was reported by Dr. S. E. Rees as follows: "There was still an area of density opposite the left hilar region, extending to the periphery of the lung. There was considerable increased density in the right hilus, with mottling extending into the pulmonary field." After death and necropsy, critical reexamination of the original roentgenograms failed to show the alterations in the heart and pericardium discovered at autopsy. Comparison of the roentgenograms taken immediately after entry and at the time the boy was allowed to go home revealed no more than possible slight enlargement of the heart, and the value of this finding was questionable, since the tube distances were not recorded and may have been different on the two occasions.

On returning home the boy was kept in bed for a short time, but since he was suffering no greater discomfort than was to be expected with the injuries known to be present, he was soon allowed to be up and about. He rapidly resumed his normal activities and vied at all times with children of his own age. Occasionally thereafter there were bouts of mild pain over the site of the injury, which were attributed, probably correctly, to pressure of the displaced ends of the ribs on the overlying muscles. The thoracic deformity persisted, and the protruding knobs at the site of the healed fractures of the ribs could be palpated. To all appearances the child was both healthy and active. In particular there was no complaint on

his part of any symptoms referable to the heart. After death of the boy the parents were closely questioned in this respect. They had noted nothing more than some shortness of breath after he had carried seven or eight armfuls of wood up a single flight of stairs. This was not of recent origin, was not progressive and seemed to have been concomitant with a rather rapid gain in weight. Since the mother was of the attentive type and always took the boy to a physician when any symptom developed, it is fairly certain that dyspnea if it existed at all must have been mild. Direct questioning revealed that there had been no pain radiating to the shoulder, arm or neck. The pain over the site of injury was not of the type originating from the heart, never being incapacitating, sharp or excruciating. The family could not recall any particular attack that clinically might fit the autopsy observations. Two weeks before death the child was examined by the same physician who attended him at the time of the accident and who had seen him from time to time in the interim. Nothing abnormal was found.

On the evening of Dec. 4, 1936, the boy retired, seemingly well, but at 4:45 a. m. he was found in bed in a dying condition. There had been no outcry, and there was very little evidence of a struggle. Emesis was noted. It was thought at first that he had choked on some food.

Postmortem Observations.—The body was 156 cm. in length and had an estimated weight of 120 pounds (54.5 Kg.). The habitus suggested juvenile hypopituitarism; the skin was white, clear, soft and hairless; the face had a pudgy appearance; the extremities seemed short in comparison to the length of the torso; the fingers and toes were stubby; the breasts were quite well developed; the genitalia seemed rather small, and there was a definite tendency toward girdle obesity with a feminine form of hips and thighs.

No evidence of injury, disease or abnormalities of development was found in the abdominal viscera.

After the skin and muscles of the anterior aspect of the thorax had been reflected, healed and overlapping fractures of the third, fourth and fifth left costochondral junctures stood out plainly. There had been medial and anterior displacement of the lateral fragments of the third and fourth ribs, which on healing had left behind projecting cartilaginous knobs 2.5 cm. in length. The fifth rib displayed only a button-like swelling at the point of the old fracture. Firm bony union had taken place in each instance. The contour of the thorax was not appreciably altered.

When the thoracic cavity was opened, the heart was seen to be displaced to the left so greatly that the apex impinged against the left lateral wall of the chest, lifting the left lung upward and posteriorly. The right cardiac border was in a line drawn perpendicularly downward from the left sternoclavicular joint. We were astonished to find that the pericardium failed to envelop the heart; this organ lay quite bare and yet possessed a smooth, glistening, thin epicardial surface save for a single milk-white plaque in the region of the right atrioventricular groove. Furthermore, the heart was not adherent to any of the adjacent structures. It was boot-shaped, measuring 10.5 cm. in the transverse diameter and 7 cm. in the vertical direction. Both ventricles appeared to be moderately enlarged, especially the right one, which, along with the right atrium, formed practically all the anterior presenting aspect of the heart. The conus arteriosus was bulging and abnormally prominent (fig. 1). A slight upward and clockwise rotation of the heart was apparent, thus placing the left ventricle posteriorly. The change in position could be accounted for by the displacement of the heart to the left and the enlargement of the right ventricle.

The apparently missing pericardium was found to have retracted upward and to the right, where it was seen to form a continuous, rolled or at times pleated band encircling the heart and in continuity with the normally and fully developed anterior mediastinal tissue. The thymus was in its usual position over the upper and anterior surface of the pericardium. The retracted and bandlike pericardium was applied snugly about the great vessels and the base of the heart; its free margins were smooth, glistening, rounded and obviously thicker than elsewhere. Anteriorly the folded membrane produced a deep groove in the main pulmonary artery just distal to its valve and coursed over the right atrioventricular sulcus

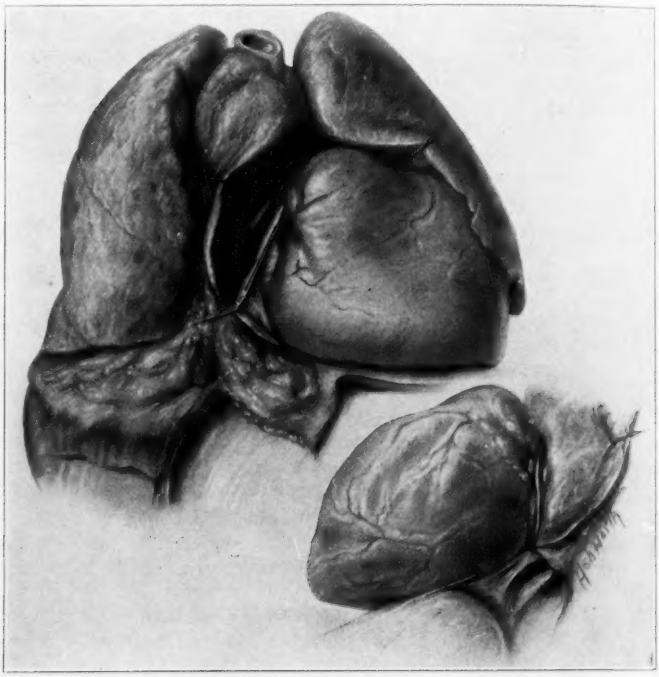

Fig. 1.—In the upper drawing is shown the anterior view of the thoracic organs and a portion of diaphragm of the 9 year old boy. The heart is displaced to the left, crowding the left lung upward. The lowermost hook pulls on the right border of the pericardium, which is seen passing upward and to the right over the pulmonary artery, greatly compressing the vessel and causing the conus arteriosus to bulge in a startling manner. In the lower drawing the left cardiac border is displayed. Covering the atrioventricular sulcus is the retracted, thickened pericardium, which has almost completely inverted the left atrial appendage.

and right atrial appendage without compressing either. To the left of the pulmonary artery the accordion-like band of pericardium narrowed down like a knife blade, first to a width of 2 cm.; finally, at the base of the heart posteriorly it existed only

as a low white ridge. The left phrenic nerve could be traced through this ridge of pericardium and into the diaphragm at the usual site; on the right side the same nerve took its normal course. The aorta, left atrioventricular sulcus and pulmonary veins, while closely approximated by the retracted pericardium, gave no indications of undue pressure on them. The superior and inferior venae cavae likewise appeared to have escaped damage. The left atrial appendage, however, was almost completely invaginated into the atrium, but it had not become adherent and was everted easily. In general, it appeared that the pericardium, which was like a purse string, was tight anteriorly and loose over the posterior surface of the heart. It is recognized that this may not have been the situation during life; but if our concept of upward rotation of the apex is correct, it would account for the appearance noted at autopsy. In this connection it should be mentioned that the body had been arterially embalmed for about ten hours prior to the postmortem examination, allowing time for good hardening of the organs and making it reasonable to assume that the positions noted were not far different from those during life. In spite of the frequent pleating of the retracted pericardial margin, adhesions had not formed, and the whole membrane, which could be unfolded easily and without undue stretching, proved to be of sufficient size to accommodate the entire heart. When the pericardium was thus reapproximated, it appeared that the line of rupture had been along the entire left border, leaving an opening just large enough to permit the extrusion of the heart.

The wall of the obviously dilated right ventricle measured 0.5 cm. in thickness. The right chambers were filled with postmortem clots. There were no lesions in the tricuspid or pulmonic valves. The interatrial and interventricular septums were intact. The superior and inferior venae cavae were unchanged. A finger passed into the prominent pulmonary conus and through the valve met with an obstruction at the point where the pericardial band passed over the artery. After thorough fixation, the pulmonary artery and its branches were examined from above after severance of the constricting band of pericardium; all contained postmortem clots. A difference in size was apparent between the right and left branches, the former having a diameter of 2 cm. and the latter a diameter of 2.7 cm. Approximately 3 mm. distal to the commissures of the cusps of the pulmonary valve, the lumen of the main artery was so constricted that a 4 mm. probe was passed with difficulty; here the wall was grooved to a depth of 3 mm. and for a width of 2 mm. The lumen at the point of narrowing contained a snugly fitting postmortem clot 4 mm. in diameter. It is reasonable to assume that the size of the clot represented the approximate caliber of the vessel at the time of death. At the point of constriction, the intima was pearly white and lacked the discoloration due to hemolysis seen elsewhere (fig. 2).

The left chambers of the heart proved to be dilated and to contain only postmortem clots. The wall of the left ventricle had a maximum thickness of 1.4 cm. The trabeculae carneae were flattened. The mitral and aortic valves were normal. When the inverted appendage of the left atrium was pushed out, it immediately resumed its natural position and shape. This feature, along with the lack of thrombus formation or adhesions, strongly suggested that the pericardium had not been in the position in which it was found for any appreciable time prior to death. The ductus arteriosus was obliterated.

The lungs displayed pronounced edema. The larger air passages, including the larynx, were patent. Aside from a mild degree of acute passive hyperemia, the other organs were unchanged.

Microscopic sections of the myocardium displayed only slight hypertrophy; no scarring such as might readily follow the healing of a cardiac contusion was discerned. In the aortic intima were several minute intimal lessions containing lipoid-filled cells.

COMMENT ON AND INTERPRETATION OF THE POSTMORTEM OBSERVATIONS

The clinical and autopsy data offer many points of interest and importance. It was recognized at the outset that the foremost problem was to establish whether the pericardial defect was of congenital or traumatic origin. Important features favoring the latter and against the former type of origin were: (1) the well authenticated clinical history and roentgenolographic proof of injury of the thorax with fracture of the left clavicle and the third, fourth and fifth ribs; (2) the absence of symptoms or signs of a pathologic cardiac condition either prior to or after the accident; (3) postmortem absence of chronic dilatation of the heart, which is often reported to occur in the presence of congenital pericardial defects; (4) acute rather than chronic passive hyperemia, as would be expected if the heart had long been dilated; (5) a normally developed mediastinum; (6) the normal position and distribution of both phrenic nerves in relation to the pericardium and

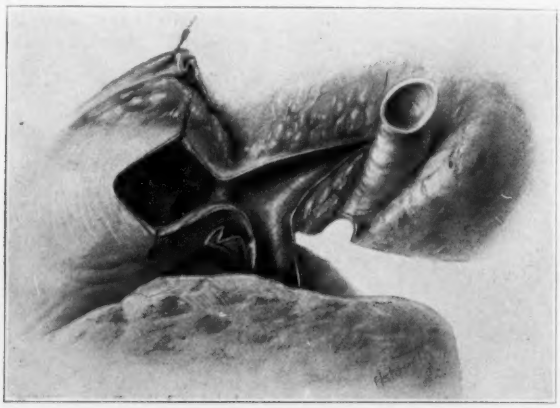

Fig. 2.—The pulmonary valve, pulmonary artery and its main branches, as viewed from above after having been hardened in solution of formaldehyde and opened. Just without the valve is a deep constriction of the main artery caused by the purse string action of the ruptured, retracted and pleated pericardium, the margins of which may be seen immediately below the vessel and again above, where a hook has been placed. Portions of the lungs and trachea are included in the drawing.

diaphragm, and (7) nonadherence of the retracted and pleated pericardium to itself or the surrounding structures and its ample size, (it accommodated the heart when stretched out and reapproximated). Plaut [2] has emphasized the position of the phrenic nerves as one point in differentiating between congenital and other forms of pericardial defects. In the congenital type the left phrenic nerve is likely to course superficially directly beneath the sternum, while the right nerve lies at a deeper level. The smaller the rudiment of pericardium, the farther to the right is the corresponding phrenic nerve displaced.[3]

The time at which herniation of the heart or retraction of the pericardium or a combination of the two took place is uncertain. The lack of pain of cardiac origin or of attacks of failure of the right side of the heart at any time after the accident and the easily retractible left atrial appendage favored terminal extrusion. Also, in some of the previously recorded examples of traumatic rupture of the pericardium in which death was not immediate, the pericardium had been bound to surrounding structures by blood clot or fibrous adhesions; nothing of the kind was present in our subject.

While the history suggested the occurrence of mild attacks of pain which could be explained by a temporary and intermittent escape of the heart through the pericardial rent, it is impossible for us to believe that the degree of obstruction of the pulmonary artery so plainly evident at necropsy could have existed for any length of time. Rather, we feel that it was the actual and immediate cause of death and could not have existed constantly during the two and a half years of life after the injury. In support of this concept were the lack of hypertrophy of the right ventricle and the presence of evidence of its acute dilatation and of generalized acute passive hyperemia. The final mechanism must have been akin to that operating in embolic occlusion of the pulmonary artery, save that the obstruction was not complete and was applied from without rather than from within the vessel. In this connection the observations of Fineburg and Wiggers [4] may be cited. In experimental obstruction of the pulmonary artery it was shown that more than 58 per cent constriction not only resulted in congestion of the right side of the heart and failure but also introduced another factor, namely, a lowered blood supply to the left side of the heart, a drop in systemic blood pressure and ischemia of the coronary arteries, thus causing dilatation and failure of the left side of the heart and an extremely rapid failure of the right side, attributable to a lack of arterial blood supply to the

2. Plaut, M.: Ueber zwei weitere Fälle von Defekt des Herzbeutels, Frankfurt. Ztschr. f. Path. **12**:141, 1913.

3. Plaut,[2] p. 146.

4. Fineburg, M. H., and Wiggers, C. J.: Compensation and Failure of the Right Ventricle, Am. Heart J. **11**:255, 1936.

myocardium. Beck's [5] triad of clinical signs of compression of the heart itself, namely, (*a*) a low arterial pressure, (*b*) a high venous pressure and (*c*) a small quiet heart, expresses the same thought in different words.

ADDITIONAL CASES

We are including references to additional cases largely because of the meager statistics relating to the effects of trauma on the pericardium. While the essential facts concerning these cases are given in the accompanying table, certain features contained therein deserve amplification.

In the majority of the cases the injuries were sustained in motor vehicular accidents, the victim being struck and knocked down or run over or both. One victim was struck almost simultaneously by two cars. Others were thrown from automobiles or pinned beneath them. Four deaths were the result of falling; 1 victim was crushed by an elevator.

The youngest patient, whose case has just been reported in detail, was 9 years of age at the time of death and the eldest 84. The age of the majority fell between 40 and 50, i. e., the years of activity in industry but of decreasing agility.

In 13 the pericardium was ruptured on the left side, mostly along the margo obtusus of the heart; in 4 the rupture was located on the right side, for the most part somewhat anteriorly; 1 patient displayed multiple lacerations, while the site of rupture in 1 case was inadequately described.

The heart was found protruding through the opening in the pericardium 7 times. In 4 cases the descriptions were vague, but from the nature of the lesions it would seem impossible for cardiac herniation to have occurred. One example is particularly interesting because of its similarity to the case just described in detail, for while death was sudden and the result of other extensive injuries, the pericardium nevertheless had slipped backward and was so tightly encircling the midportion of the left ventricle that the muscle at this point was both depressed and blanched. In another case of pericardial rupture, the interatrial septum was torn across, and in another contusion of the myocardium was displayed.

With the 1 exception, none of the victims survived for any appreciable time, all of them dying as a result of multiple injuries almost at once.

As a rule, the side on which the pericardium was torn, whether right or left, corresponded to the side from which the force came. Two cases proved to be exceptions to this rule. In attempting to classify these, however, one familiar with vehicular accidents can readily under-

5. Beck, C. S.: Two Cardiac Compression Triads, J. A. M. A. **104**:714 (March 2) 1935.

Summary of Data on Twenty-Two Cases of Traumatic Rupture of the Pericardium Encountered in Routine Necropsies

Case No.	Age, Years	Cause	Site of Injury of Pericardium	Perforation of Heart	Direction of Force	Accompanying Injuries	Mechanism of Rupture	Comments
1	14	Thrown from car	Left	No	Left	Rupture of lung, liver, spleen and adrenals	Compression	5 cm. tear in pericardium
2	24	Elevator	Anterior and right posterior	No	Uncertain	Rupture of lung, liver and inferior vena cava	Compression	Heart herniated
3	?	Street car	Left and inferior	No	Left	Rupture of spleen and left lung	Laceration ?	No herniation of heart
4	55	Fell 2 stories	Left base	Yes	Uncertain	Rupture of lung; fat embolism	Laceration	Laceration due to sternal fragments
5	45	Crushed by auto	Left	Yes	Uncertain	Fractured ribs; hemorrhage	Laceration	Heart herniated
6	72	Automobile	Left	Yes	Uncertain	Fracture of spine and sternum; rupture of liver	Laceration	Torn inferior vena cava
7	84	Run over by car	Right anterior	Yes	Left	Fracture of spine and ribs	Laceration	Torn inferior vena cava
8	70	Struck by 2 cars	Anterior	Yes	Right	Injury of lungs, liver, diaphragm, spine and ribs	Perforation	Heart herniated ?
9	44	Fall	Right anterior	Rupture	Uncertain	Rupture of diaphragm; right hemothorax	Compression	No ribs fractured
10	56	Run over by car	Anterior	Yes	Left	Rupture of lung, spleen and liver; fracture of ribs	Perforation ?	Heart herniated ?
11	45	Fell 6 stories	Several	Yes	Left	Fracture of sternum, ribs and skull	Laceration	Heart not protruding
12	?	Automobile	Anterior	Rupture	Right	Fracture of right ribs and legs	Compression	No protrusion of heart
13	78	Automobile	Posterior left	No	Left	Fracture of ribs and spine; rupture of liver and spleen	Compression	No protrusion of heart; 10 cm. pericardial tear
14	40	Fell 6 floors	Left	No	Left	Fracture of spine and ribs; rupture of left lung, liver and kidney	Compression	Heart herniated; 8 cm. pericardial tear
15	18	Automobile	Right anterior	No	Right	Rupture of liver, spleen, kidney and diaphragm	Compression	Heart not herniated; no fractured ribs
16	42	Automobile	Inadequately described	No	Uncertain	Rupture of liver, lung and left kidney	?	Small pericardial tear
17	19	Automobile	Left; pulmonary vein downward	Yes	Left	Rupture of spleen; fracture of left ribs; laceration of left lung	Laceration	Torn pumonary veins
18	35	Automobile	Left side	No	Right	Rupture of liver, diaphragm and interauricular septum	Compression	Rupture on side opposite applied force
19	45	Fell 3 stories	Left	No	Uncertain	Fracture of ribs and sternum	Compression	Heart herniated
20	65	Automobile	Left	No	Left	Rupture of aorta; superficial laceration of vena cava; fracture of ribs and sternum	Compression	Heart herniated through tear and strangulated
21	60	Automobile	Left	No	Probably left	Rupture of brain stem, liver, kidney and spleen; fracture of ribs	Compression	Herniation of heart
22	9	Run over by auto trailer	Left	No	Left	Fracture of left ribs and clavicle	Compression	Herniation of heart; strangulation of pulmonary artery

stand the difficulty encountered in determining solely from a written record the exact direction from which multiple forces were applied.

In the main it appears that two mechanisms of pericardial rupture exist: (1) compression and (2) laceration or puncture by the ends of fractured bones. A combination of the two is likewise possible, the pericardium bursting under the effects of pressure alone and before the ribs give way; but in such cases, particularly when the pleura was torn by the fractured ribs in any situation in which it would be at all possible for spicules of bone to have produced the holes in the pericardium, we have considered it best to regard the lesions as penetrating wounds due to the ends of bones. On the other hand, in certain cases in which the fractured ribs were so located that penetration of the pericardium was impossible, it has seemed logical to classify the condition as a pure compression rupture of the pericardium.

REVIEW OF THE LITERATURE

One of the earliest, certainly the most exhaustive and even today still one of the valuable contributions on the subject of traumatic cardiac and pericardial wounds was published by Fischer,[6] in 1868. The purpose of Fischer's paper, based on 452 wounds (401 of the heart and 51 involving the pericardium), was to refute the then generally held belief that wounds of the heart and its enveloping membranes were absolutely fatal and, further, to catalog the diagnostic symptoms of such conditions. Personal cases and those he found reported in the literature were grouped according to the etiologic factors, the site and depth of the wounds and the duration of life after injury. We mention the manner of arrangement because it explains the lack of strict chronologic order in the numbering of the case reports of pericardial rupture cited by Fischer, abstracts and excerpts from which are given herewith. The case numbers in parentheses are Fischer's numbers. All instances of perforation of the pericardium by sharp instruments or bullets are intentionally omitted.

CASE 1 (case 374).—(Hewett, P.: *London M. Gaz.* **4**:870 [May 14] 1847.) We were fortunate in obtaining the original article, and the abstract is from that source rather than from Fischer's article. Five instances of rupture of the heart and vessels were presented. Of these, only the second was an example of pericardial rupture. A man aged 53 was brought into St. George's Hospital dead, the report being that he had been kicked in the chest by a horse with enough force to send him backward several feet. The passersby ran to the man's assistance, but he was dead. At necropsy no marks of violence were observed, but when the skin was removed from the chest, some extravasated blood was found in the soft tissues. In the second piece of the sternum was a transverse fracture, without displacement, despite the laceration of the periosteum on both sides. The left second to sixth

6. Fischer, G.: Die Wunden des Herzens und des Herzbeutels, Arch. f. klin. Chir. **9**:571, 1868.

ribs were fractured in two places, close to the cartilages and near the spine; on the right side the second to fourth ribs were fractured about 3 inches (7.6 cm.) from their cartilages. The pericardium was filled with blood, and an extensive laceration was seen on the left side. Old adhesions between the lung and the pericardium prevented the escape of blood into the pleura. The right ventricle of the heart presented a transversely directed laceration of its anterior surface at the junction with the pulmonary artery, through which the tip of the index finger was easily passed. The lungs were not traumatized; the other viscera were not examined.

Case 2 (case 375).—(Vater, C.: Ephemer. nat. curios. Dec. III. ann. IX and X, Nuremburg, Frankfort and Leipzig, 1706, obs. 164). A 30 year old woman was crushed against a wall by a wagon (1695). There were fractures of the first and second left ribs near the sternum and a fracture of the left clavicle. The pericardium was only slightly injured, but the right ventricle was torn at the top, with much blood in the pericardium. It was clearly stated that the rupture was not produced by the fractures but from compression of the thorax.

Case 3 (case 376).—(Niemann, A.: *Ztschr. f. d. Staatsarznk.*, 1861, p, 326.) The victim had been run over. The pericardium had a long tear near the vena cava, and the right ventricle had a tear near the attachment of the vena cava. There was much blood in the mediastinum, and the pericardial sac was distended with blood to four times its natural size.

Case 4 (case 379).—(Dupuytren, G.: *Clin. chir.* **2**:215, 1839.) A man aged 41 years was pressed against a wall by a wagon tongue, sustaining fractures of several ribs and a diagonal break in the sternum at the juncture of both the upper and the lower third. The upper fragment was forced deep into the mediastinum. The man was relatively well until the fourth day after injury, when oppression and a small pulse beat were noted. His condition ranged from suffocation to improvement for ten days. Subcutaneous emphysema was lacking; there was an ecchymosis extending from the chest to the hip. Death due to pericarditis occurred on the twelfth day. It was found that the upper fragment of the sternum had penetrated the pericardium and torn a third of the way through the right ventricle. There was bloody serum in the right pleural cavity, and old strong adhesions were present between the pleurae.

Case 5 (case 380).—(Elleaume, A. H.: Essai sur les ruptures du cœur, Thesis, Paris, no. 186, 1857, p. 14.) A man 20 years of age fell from a tree and died within a few minutes. There was rupture of the pericardium and of the left ventricle.

Case 6 (case 391).—(Morel-Lavallée, V. A. F.: *Gaz. d. hôp.*, 1860, p. 19; 1864, pp. 46, 48, 51 and 53.) [7] The first case, described in the paper of 1860, concerned a carpenter who fell a distance of 6 meters, striking on his left side. He was rendered unconscious and when seen was in shock. Later he became lucid, but after five hours, during which vomiting took place, he lapsed into unconscious-

7. The original articles were abstracted by us. Evidently the same cases referred to by Fischer were reported in the following articles: Laceration of the Pericardium and Fracture of the Skull, Bull. Soc. de chir. de Paris **1**:64, 1860; Rupture of the Pericardium: Water-Wheel Murmur; Mill Murmur, Gaz. méd. de Paris **19**:695-729, 771 and 803, 1864.

ness. Examination the following day disclosed injury to the head, fracture of the sternoclavicular joint or clavicle and indications of injury over the precordium. Lavallée said he heard a loud "double systolic, 'water-wheel,' murmur;" the sounds were alternately loud and soft and sharply interrupted, like the impact of water on the blades of an overshot water wheel. He concluded that this could have been made only by fluid or air or both which was being drawn in and out of the pericardial sac and that a pleuropericardial communication was necessarily present. The man lived for three days. Postmortem examination disclosed a fracture of the cartilaginous portion of the third rib, without displacement, and rupture of the pericardium along the left border 3 cm. above the apex; the tear had irregular edges, was round and permitted the insertion of the little finger. Fluid was present in both pleural and pericardial sacs, thus confirming the observer's contention. Specific mention was made that continuity of the parietal pleura beneath the fractured rib persisted. Fracture of the skull with subdural hemorrhage was the direct cause of death.

Comment.—In his discussion the author stressed the value of *Bruit de roue hydraulique* or *bruit de moulin* as a diagnostic sign of pericardial rupture. This has not been mentioned by any subsequent writer. As to the mechanism of production of rupture of the pericardium, Lavallée said he felt that the lungs and heart were crushed against the vertebrae during the impact and that the tear was produced by shearing or rubbing of the membrane against the bone.

This case and 2 others formed the basis of a publication appearing in 1864. Again Lavallée mentioned having heard the "water wheel murmur." One of the new cases appears to us to have been an example of pneumohydropericardium and is not included here. The other (Fischer's case 439) was that of a workman who fell three stories onto some prominence and then to the ground, sustaining a compound fracture of the left leg, left hemiplegia and shock. Hematuria was noted. Icterus appeared shortly, suggesting rupture of the liver. Heard most distinctly over the nipple region at each seventh, fifteenth and twentieth pulsation and repeating itself four or five times was a murmur like the sound produced by blowing in an empty bottle. It vanished when the patient was upright, reappeared when he was prone and disappeared after five days, when a precordial rub developed. The positive diagnosis of a pleuropericardial communication was confirmed at autopsy, nine days after the accident, by the finding of a most remarkable rupture of the pericardium. It consisted of five great tears which left webs of pericardium and holes, the largest of which admitted a whole hand. It measured 10 by 13 cm. Herniation of the heart was noted. There were no demonstrable fractures of the ribs; the findings in other parts of the body were insignificant. In this paper the author suggested the possibility that rupture had been produced by vibration, although he again said he considered that friction may have been responsible.

These 2 cases are most remarkable because the patients were seen by the same physician, who established the correct diagnosis of a rare

lesion during life. The second example is noteworthy on account of the extensiveness of the pericardial damage and further because it demonstrates that the pericardium is not an indispensable structure, since the patient survived for a number of days. Finally, it was Lavallée who first ventured a plausible explanation of the cause of pericardial rupture.

CASE 7 (case 392).—(Loir, J. N.: Dissertation et propositions sur quelques points d'anatomie de physiologie et de pathologie, Thesis, Paris, no. 45, Paris, Méquignon-Marvis, père & fils, 1835.) A driver 23 years old was caught between the wheels of two wagons; he quickly lost consciousness and died. There were fractures in the posterior halves of the eighth and ninth ribs and blood in the left pleura and the pericardium, where a 2 inch (5 cm.) opening was seen. On the posterior surface of the heart was a 1½ inch (3.8 cm.) wound communicating with both chambers. The injury had been caused by the sharp fragments of the eighth rib. The spleen was ruptured. (Fischer stated that this case was cited by Choisy from Bouillaud [Bouillaud, J. B.: Traité clinique des maladies du coeur, Paris, J. B. Ballière, 1835, vol. 2, p. 499] and in the works of Dupuytren and Marx [Dupuytren, G.: Leçons orales de clinique chirurgicale, Paris, Germer-Baillière, 1839, vol. 2, p. 213.])

CASE 8 (case 395).—(Duverney, J. G.: Traité des maladies des os, Paris, De Bure l'ainé, 1751, vol. 1, p. 275.) A man fell on a stone while bowling, splintering and crushing the body of the sternum and tearing the pericardium and right auricle.

CASE 9 (case 399).—(Wilkin and Lees: *Dublin J. M. Sc.* **2**:174, 1837.) A brewer was run over; he got up and drove on for another hour and then went to the hospital, complaining of pain. He died immediately after turning on his side. There was a fracture of the fifth rib, the end of which penetrated the pericardium and right auricle, plugging the hole in the former but not in the latter. Apparently both were closed at first and became loosened when he was lying down.

CASE 10 (case 411).—(Gamgee, J. S.: Researches in Pathological Anatomy and Clinical Surgery, London, H. Baillière, 1856.) A man of 38 fell from a wagon. The pericardium was torn anteriorly, a rent the size of a goose quill was seen in the auricle and the liver was torn. The heart was otherwise normal.

CASE 11 (case 416).—(Dickinson: *London M. Times*, Jan. 31, 1863.) A child of 5 years was run over and brought into the hospital dead. There were no external injuries, but the pericardium was full of blood, which issued from a tear in the tip of the heart. Both ventricles were open, and the heart was considerably torn, as was also the pericardium. There were no fractures.

CASE 12 (case 417).—(St. Thomas' Hospital, London; von Chelius, M. J.: A System of Surgery, translated by J. F. South, Philadelphia, Lea & Blanchard, 1847, vol. 1, p. 546.) A man was run over and then walked about one hundred steps. He died in about nine hours of suffocation. There were fractures of the first two ribs on the right side and of the upper five ribs on the left side. A sharp end had been forced into the pericardium and had injured the heart near the tip. Both the pleurae and the pericardium contained blood. The right side of the diaphragm and the apex of the left lung were torn.

CASE 13 (case 420).—(Mayer: *Med.-chir. Ztg.*, Aug. 31, 1835.) A farmer was thrown from a raft by a falling log without being touched by it. He fell into the water and although brought up immediately proved to be dead. There was 5 pounds (2.3 Kg.) of blood in the thorax. A tear was seen in the pericardium near the attachment of the aorta; another occurred at the tip of the heart. The myocardium was healthy.

CASE 14 (case 422).—(Casper, J. L.: Practischer Handbuch der gerichtlichen Medicin, Berlin, A. Hirschwald, 1857, p. 122.) A man aged 24 was hurled with great force from a wagon against a poplar tree. Outward evidence of injury was lacking. The spinous process of the first thoracic vertebra was broken. The heart was completely torn from the vessels and lay free in the thoracic cavity. The pericardium was likewise wholly divided. The heart substance was normal. Three quarts (2,840 cc.) of blood occupied the left side of the thoracic cavity. The lungs and liver were torn.

CASE 15 (case 423).—(Casper, J. L.: Klinische Novellen zur gerichtlichen Medicin, Berlin, A. Hirschwald, 1863, p. 347.) A man was instantly killed by a falling iron beam. The left side of the chest was completely crushed, and there were six or eight tears in the left lung, which were not produced by the fractures. The pericardium was torn its full length, and the heart, separated from its great vessels, lay free in the pericardial sac.

CASE 16 (case 425).—(Flügel: *Aerztl. Int.-Bl.*, 1859, no. 26.) A boy 17 years of age was caught in a gear and was dead when rescued. A few drops of blood issued from the nose and mouth; there were abrasions on the body. The fourth rib was fractured near the nipple. Both pleural sacs were filled with blood. The pericardium displayed a posterior tear through which the heart herniated. Tears existed in the lungs, liver and spleen.

CASE 17 (case 426).—de Berghes: *Wchnschr. f. d. ges. Heilk.*, 1844, no. 20, p. 326.) A man was crushed under a falling tree. The thorax and abdomen were split so that a large part of the viscera came out, tearing the heart from its attachment and allowing it to fly for a distance of ten steps from the body. The heart was lacerated in several places superiorly, so that the fingers could be inserted into the ventricles; no traces of vessels or valves remained on the organ. It should be noted that although no mention of the pericardium was made, it must have been ruptured.

CASE 18 (case 430).—(Sanson, A.: Plaies du coeur, Thesis, Paris, no. 259, 1827, obs. 24, p. 34.) A man of 40 years was struck over the chest by a wagon tongue, which fractured several ribs and the sternum. He was found in shock and was treated by bandaging and bleeding. Death supervened on the thirteenth day. The fourth to sixth ribs were broken 3 inches (7.6 cm.) from the sternum, and in the latter was a transverse fracture. A pint (475 cc.) of bloody serum was present in the right pleura. The upper fragment of the sternum was forced inside the pericardium, and in this region there was a nonpenetrating wound, measuring about 1 inch (2.5 cm.) in length, directed transversely on the surface of the heart. The pericardium was reddened and had adhesions.

CASE 19 (case 432).—(Watson: *New York J. Med.*, vol. 3, p. 351.) In this case there was a fracture of the sternum which tore the pericardium but compressed the heart only slightly.

CASE 20 (case 435).—(Irving, J.: Rupture of the Heart from Accident, *Lancet* **1**:241, 1859. Fischer listed only the reference; we have made the abstract.) A boy of 16 years was run over by an empty wagon, the wheels crossing the chest; death was instantaneous. The face and body generally appeared pallid; one or two of the spinous processes of the dorsal vertebrae were fractured; the fifth and tenth right ribs were broken. The pericardium showed a tear, which barely admitted the forefinger, communicating with the right pleura. The heart was the seat of three ruptures; there were three lacerations in the lower lobe of the right lung opposite the fractured ribs. Irving said he felt that the first wheel must have come on the heart when the ventricles were full and must have burst them, whereon the pericardium immediately distended and was ruptured by passage of the second wheel.

CASE 21 (case 436).—(Christison, cited by Watson: *New York J. Med.*, vol. 3, p. 96.) Rupture in this case was due to a fall. No details were given.

CASE 22 (case 437).—(Christison.) In this case rupture was due to a blow; no further information was given.

CASE 23 (case 438).—(Costa de Sarda: *Gaz. d. hôp.* **26**:413, 1853.) A 45 year old man fell from the fourth floor of a house, sustaining a rupture of the entire left side of the pericardium, extrusion of the heart and three fractures of the sternum, with the first fragment pressing posteriorly, resulting in a tear in the ascending aorta, lung and diaphragm. Additional fractures and dislocations were present. He died at once.

CASE 24 (case 440).—(Lente, F.: *New York J. Med.* **17**:171, 1851.) A man aged 36 was struck by a bale of hay on board a ship and was precipitated 20 feet (6 meters) into the hold. The results included a comminuted fracture of the sternum, laceration of the pericardium, contusion of the heart and fracture of a cervical vertebra.

CASE 25 (case 441).—(Casper, J. L.: Practisches Handbuch der gerichtlichen Medicin, Berlin, A. Hirschwald, 1857, p. 124.) A 44 year old man fell 46 feet (14 meters) into a cellar and probably died at once. The pericardium was torn along its entire length, but the heart was not injured. The liver and spleen were lacerated, the ribs were "bent in" and the skull was fractured.

CASE 26 (case 442).—(Hermann, J.: *Oesterr. med. Wchnschr.*, 1846, p. 347.) There was rupture of the pericardium and diaphragm allowing herniation of the small bowel into the thoracic cavity.

CASE 27 (case 444).—(Stokes, W.: *Edinburgh M. J.*, July 1, 1831; *London M. Gaz.*, July 30, 1831, p. 560.) This case was not confirmed by autopsy but is of great interest clinically. It is discussed at end of this paper.

CASE 28 (case 449).—(Morel-Lavalleé, cited by Casper, J. L.: Practisches Handbuch der gerichtlichen medicin, Berlin, A. Hirschwald, 1857.) A patient who had a water wheel murmur recovered; autopsy was not performed. We are inclined to feel that this was an example of pneumohydropericardium, although Morel-Lavallée made a clinical diagnosis of rupture of the pericardium.

CASE 29.—(This case was not included in Fischer's review. It was reported by Duka[8] in 1862.) A man aged 65, a Mohammedan, fell during a scuffle and

8. Duka, T.: A Case of Rupture of the Right Ventricle of the Heart and Pericardium, Indian Ann. M. Sc. **8**:257, 1862.

suddenly expired. The left pleural cavity and pericardial sac were distended with blood. A few "lines" above the apex of the heart and covered by the lower lobe of the left lung was a small horizontally directed aperture in the pericardium, with seepage of blood into the torn margins of the membrane. The wall of the right ventricle had two rents, one complete and the other only partial. The heart displayed fatty degeneration and extensive atheromatous deposits in the main arteries. Rupture of the pericardium was mentioned as the most remarkable feature of the case, but the reason therefor was not stated.

CASE 30.—(Damman,[9] 1872.) In this instance, pericardial rupture was observed at autopsy. The person had fallen out of a *Greitjearraa* (a local type of conveyance in Cape Town, South Africa), and died immediately. In a case in which the patient was observed clinically, Damman suggested the possibility of ruptured pericardium; permission for necropsy was denied, and the diagnosis could not be confirmed.[10]

CASE 31.—(Joubin,[11] 1873.) The patient was struck on the chest and died. A rent in the pericardium was found at the postmortem examination.

CASE 32.—(Lewtas,[12] 1876.) A coolie fell about 40 feet (12 meters) into the hold of a ship; death ensued two hours later. There was extensive subcutaneous emphysema; fractures were found in the left clavicle and in many of the ribs on the left side, producing many wounds in the left lung. In the right side of the pericardium was a 2 inch (5 cm.) rent; the edges were discolored with blood which had extravasated into the membrane. Through the opening the heart could be seen in its normal position. Another and smaller rupture of similar appearance was found in the left side of the pericardium close to the apex of the heart. The pericardial sac was devoid of blood, but about 6 ounces (178 cc.) that may have come from the torn membrane lay in the right pleural sac. The right ribs and lung, liver and spleen were uninjured. Lewtas had never before encountered a pericardial rupture.

CASE 33.—(Allan,[13] 1878.) A man aged 48 was crushed when a bale of cotton struck his back. Considerable hemorrhage from the urethra warranted a clinical diagnosis of fracture of the pubic bone with rupture of the membranous urethra. He had great pain in the cardiac region, incessant painful cough and an anxious expression. Elevation of the temperature and slight pneumonia persisted for a week. The temperature returned to normal and continued thus for fifteen days, followed by signs of pleurisy and pericarditis. Death supervened one month after his admission to the hospital. At necropsy bilateral serofibrinous pleuritis, pulmonary congestion and edema and a pericardial tear along the whole left border were present. When the anterior part of the left lung was lifted from the peri-

9. Damman: Verhandel. v. h. Genootsch. t. Bevord. d. Nat. Genees- en Heelk. te Amsterdam **3**:13, 1872-1873.

10. This case report was translated for us by Dr. J. G. Huizenga, Holland, Mich.

11. Joubin, F.: De la déchirure du poumon sans fracture de côte correspondante, considerée au point de vue de son mécanisme et de ses symptômes, Thesis, Paris, no. 304, 1873; cited by Shackelford, R. T.: Hydropneumopericardium, J. A. M. A. **96**:187 (Jan. 17) 1931.

12. Lewtas, J.: Rupture of the Pericardium, Indiana M. Gaz. **2**:296, 1876.

13. Allan, J.: Rupture of the Pericardium, Fracture of the Pelvis and Rupture of the Urethra, Lancet **2**:331, 1878.

cardium it was found to be adherent by its anterior margin; inferiorly the lung was thinned out and insinuated around and behind the apex of the heart. When the adhesions were broken up, the pericardium proper proved to be entirely absent from the left side of the heart, and the internal (medial?) surface of the left lung acted in its place. It was then observed that the anterior margin of the left lung adhered to the retracted right border of the torn pericardium. The left side of the lacerated pericardium appeared as a band ¾ inch (1.9 cm.) broad, running parallel with the long axis of the body behind the middle part of the heart, and presented a free border. The portion of pleura in contact with the left side of the heart was unaltered. The improvised pericardium contained 1 ounce (30 cc.) of turbid serum, with a layer of recent lymph on the heart and parietal surfaces. Concomitant injuries were fractures of the os innominatum, separation of the sacroiliac synchondrosis and rupture of the membranous urethra.

Case 34.—(Reynier.[14]) In this case trauma to the chest was incurred without injury to the heart, although there was a wide communication between the pericardial sac and one of the pleural cavities. Death took place after three hours.

Comment.—After Fischer's [6] review of the literature, the next one was made by Schuster,[15] in 1880. The following abstracts were obtained from this source, and the references are for the most part as he gave them:

Case 35.—(Biermer: *Schweiz. Ztschr. f. Heilk.* **2**:146, 1863.) A 33 year old man was run over by a heavy wagon and died twenty-two hours later. Rupture of the pericardium, a tear in the right auricle, numerous fractures and rupture of the left bronchus were present.

Case 36.—(Bernt: *Beitr. z. ger. Arzneikunde*, vol. 5, p. 86.) A man of 58 fell from a choir loft, lacerating the pericardium from top to bottom, tearing the right auricle, separating the heart from its great vessels and fracturing the sternum, nearly all the ribs and many other bones.

Case 37.—(Bernt, J.: Visa reperta, Vienna, J. B. Wallishausser, 1827-1845, vol. 3, p. 286.) In this case a 1 inch (2.5 cm.) tear in the pericardium, right atrium and septum; fractures of the arms and several ribs, and rupture of the liver occurred in a 47 year old man as a result of a fall.

Case 38.—(Bernt, J.: Visa reperta, Vienna, J. B. Wallishausser, 1827-1845, vol. 3, p. 328.) A woman of 70 was run over; as a result there were several tears in the pericardium; rupture of the right atrium, superior vena cava, diaphragm, liver and stomach, and fracture of several ribs and the right clavicle.

Case 39.—(Dehenne, A.: *Rec. d. mém. de méd. mil.* **34**:377, 1878.) Dehenne described a case of rupture of the heart and pericardium in a soldier who fell from a horse and died within an hour. The left arm was broken.

14. Reynier, P.: Recherches cliniques et expérimentales sur le bruit de moulin dans les traumatismes de la poitrine, Thesis, Paris, no. 14, Paris, A. Parent, 1880; cited by Martin and Mazel.[20]

15. Schuster: Ueber die Verletzungen der Brust durch stumpf-wirkende Gewalt, vom gerichts-ärztlichen Standpunkt, Ztschr. f. Heilk. **1**:417, 1880.

CASE 40.—(Maschka, J.: Pr. Vierteljahrs., vol. 73, p. 121.) A laborer was crushed between two trains, with resultant fracture of the sternum and all the ribs and rupture of the pericardium, left ventricle and upper lobes of the lungs.

CASE 41.—(Pamard, cited by Dehenne, A.: *Rec. de mém. de méd. mil.* **34**: 377, 1878.) A man 39 years old was crushed under a heavy load and died immediately. The pericardium was ruptured, the right ventricle was torn and many ribs were fractured.

CASE 42.—(Taylor, A. S.: A Manual of Medical Jurisprudence, London, J. Churchill, 1844, vol. 1, p. 639.) A child was instantly killed when run over. The pericardium and heart were torn for their entire length. External signs of injury were absent.

CASE 43.—(Bernt, J.: *Beitr. z. ger. Arzneikunde*, vol. 4, p. 100.) When pitched from a wagon by a bolting horse, a 48 year old man died immediately. Autopsy showed fracture of the sternum, several ribs and one vertebral body and laceration of the pericardium and of both cardiac ventricles.

CASE 44.—(Bernt, J.: Visa reperta, Vienna, J. B. Wallishausser, 1827-1845, vol. 2, p. 314).) A man 48 years of age fell from a height, rupturing the pericardium, interatrial septum, lungs, liver and spleen. The sternum and several ribs were fractured.

CASE 45.—(Casper, J. L.: Practisches Handbuch der gerichtlichen Medicin, Berlin, A. Hirschwald, 1857, vol. 2, p. 256.) This person was run over by a railway train. The pericardium and numerous other organs were ruptured, but the heart was spared. There were many fractured bones.

CASE 46.—(Bernt, J.: Visa reperta, Vienna, J. B. Wallishausser, 1827-1845, vol. 2, p. 302.) A manservant of 44 years was run over. The pericardium had a 4 inch (10 cm.) tear; the heart was undamaged. A bruise was seen on the chest, ribs were fractured and several organs contained lethal ruptures.

CASE 47.—(Bernt, J.: Visa reperta, Vienna, J. B. Wallishausser, 1827-1845, vol. 2, p. 332.) A 44 year old man fell from a roof, tearing the pericardium from top to bottom, crushing the skull and breaking several ribs and the sternum.

CASE 48.—(Gérin-Roze, cited by Dehenne, A.: *Rec. de mém. de méd. mil.* **34**:377, 1878.) This person fell from a third story, rupturing the heart, aorta and pericardium.

CASE 49.—(Devergie, M.: Médecine légale, Paris, Germer-Baillière, 1836, vol. 2, p. 376.) A man of 30 years who had been in a drunken brawl and probably was struck in the chest died quickly as a result of a rent in the pericardium at the root of the great vessels and rupture of the intrapericardial portion of the pulmonary artery. There was a stab wound in the neck.

CASE 50.—(Rose,[16] 1884.) This author saw 2 patients with traumatic injury of the chest resulting in combined rupture of the heart and pericardium; 1 patient lived four days and the other for several hours.

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16. Rose, 1884, cited by Loison: Rev. de chir. **19**:49, 1899; cited by Bright, E. F., and Beck, C. S.: Non-Penetrating Wounds of the Heart: A Clinical and Experimental Study, Am. Heart J. **10**:293, 1935.

CASE 51.—(O'Brien,[17] 1893.) A woman fell 8 feet (244 cm.) into the water and was struck by a ship's propellor. Examination disclosed ecchymoses over the chest, fracture of the sternum between the fourth and fifth ribs and a transverse laceration of the heart and pericardium. The ribs were uninjured.

CASE 52.—(Hutchinson,[18] 1894.) A man of 59 was kicked in the chest by a horse, and a precordial hematoma developed. The skin was unbroken. Signs of severe shock were evident, and death ensued after four hours. Autopsy revealed no fracture of the sternum or ribs; the anterior mediastinum was filled with blood clot which had issued from a rent in the front part of the pericardium; a second tear communicated with the pleural cavity. The heart was not displaced and appeared to have stopped in diastole. At the apex of the right ventricle was a rupture less than ¼ inch (0.6 cm.) in diameter. Beneath the epicardium, between the rupture and the ventricular septum, was a small ecchymosis. Hutchinson said he thought that the pericardial rupture by preventing tamponading of the heart delayed death.

CASE 53.—(Bergmann,[19] 1901.) A young man was apparently crushed between two railroad cars and died en route to the hospital. To the left of the sternum was an abrasion a few centimeters in extent. The left pleural cavity contained clotted blood. None of the bones of the thorax were fractured. The pericardium was torn, and the heart, which had herniated through the rent, lay in the left pleural sac. Both ventricles were torn at the base, the auricles were also open, and the organ remained attached only to the great vessels. The other organs were said to have been uninjured.

CASE 54.—(Martin and Mazel,[20] 1914.) A man was found lying on a railway track. He was semicomatose or unconscious and died after three days. Subcutaneous emphysema developed over the upper part of the thorax. The presence of premastoid ecchymosis led to the suspicion that the skull was fractured. No attention seems to have been paid to the pulse or to the heart. When the sternum was removed, the pericardium was seen to be torn through the whole left lateral line and anterior to its insertion in the diaphragm, some vestiges of the latter remaining in the form of dark ecchymotic areas. The posterior surface at the level of the interpulmonary area was intact. Of the anterior surface, only a strip remained, covering just the right auricle and ventricle; this had a much heavier consistency than normal pericardium; the free end was frayed and fringed. In addition to the traumatic lesions, inflammation, evidenced by fibrinous exudate in typical cor villosum arrangement, existed both over and beneath the lacerated pericardium. Fibrinous pleuritis complicated multiple perforating fractures of the sixth to the ninth left ribs. The heart and lungs had escaped traumatization.

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17. O'Brien, C. M.: Traumatic Rupture of the Heart Consequent on Fracture of the Sternum, Brit. M. J. **2**:843, 1893.

18. Hutchinson, F.: Case of Traumatic Rupture of the Heart, Brit. M. J. **2**:1427, 1894.

19. Bergmann: Ein Fall von subkutaner traumatischer Ruptur des Herzens und Herzbeutels, Monatschr. f. Unfallh. **8**:15, 1901.

20. Martin, E., and Mazel, P.: Un cas de déchirure traumatique du péricarde sans lésion du cœur avec pleuro-péricardite consécutive, Arch. d'anthropol. crim. **29**:754, 1914.

CASE 55.—(Kellert,[21] 1917.) A man aged 44, an Italian, was buried up to the waist in a sand bank cave-in. Necropsy, eight days later, revealed five small abrasions on the left anterior part of the chest. The sternum and ribs were intact. The right pleural sac was obliterated by old adhesions. The left lower part of the pericardium presented a ragged opening 4 cm. in diameter; the pericardial sac was filled with clotted blood and communicated with the left pleural cavity. The heart lay to the left of the midsternal line and was twisted slightly from left to right. There was a large amount of firm blood clot adherent to the anterior and right lateral surfaces; near the apex on the right posterior surface was a ragged linear lacteration of the heart, with blood-stained margins, allowing free communication with both ventricles.

CASE 56.—(Doughty,[22] 1923.) A housewife 35 years of age had been knocked down by an automobile four days previously. She sought attention because of dyspnea when lying down. Choking and a sensation of fulness in the hypochondrium while eating were additional complaints. Physical examination showed pronounced orthopnea without cyanosis. The apex beat was in the sixth interspace 4 cm. to the right of the midline. The left cardiac border was 2 cm. to the left of the midline. A systolic murmur was audible over the apex. The pulse rate was 120 and the blood pressure 132 systolic and 84 diastolic. Inspection of the thorax showed limited movement of the left side. The left dome of the diaphragm was elevated 3 cm. and had respiratory excursion of 3 cm., in contrast to that of 6 cm. on the right side. Fluoroscopic examination confirmed the existence of dextrocardia, although the aortic arch was in the normal location. After a week of observation, with progressive discomfort, laparotomy was attempted under local anesthesia, but the patient soon became unmanageable and expired suddenly as chloroform inhalation was begun.

At postmortem examination a linear tear of the right side of the pericardium was found, and through this the heart protruded into the right pleural cavity. A fibrinous exudate was present between the epicardium and the pleura. The left leaf of the diaphragm was ruptured, and through it the stomach and some of the small bowel protruded into the pleural cavity. The condition of the ribs and sternum was not mentioned but in a personal communication to us (Aug. 30, 1937) Doughty stated that he was certain none of the ribs were fractured.

CASE 57.—(Haberda,[23] 1927.) Two cases were mentioned, that of an infant of 8 months (the mother had jumped with the baby from a third story window to the pavement below) and that of a woman of 34 who had thrown herself from the second floor. The thoracic wall of the infant was not injured; the pericardial laceration was located on the anterior surface and was accompanied by hemorrhage into the mediastinum. In the woman both the sternum and the heart were uninjured, there was no hemorrhage into the mediastinum and only the internal layer of the pericardium was torn.

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21. Kellert, E.: Traumatic Rupture of the Heart: Report of a Case with Uninjured Chest Wall, J. Lab. & Clin. Med. **2**:726, 1917.

22. Doughty, J. F.: Traumatic Rupture of the Pericardium with Resulting Dextrocardia Complicated by Rupture of the Diaphragm and Liver, J. A. M. A. **81**:1784 (Nov. 24) 1923.

23. Haberda, A., in von Hofmann, E.: Lehrbuch der gerichtlichen Medicin, ed. 11, Berlin, Urban & Schwarzenberg, 1927, p. 584.

CASE 58.—(Spitzmüller,[1] 1928.) A janitor 40 years old fell 15 meters through a skylight, striking on the sacrum. Consciousness was retained; he was shocked and complained of excruciating pain in the chest and abdomen and painful respiration. The pelvis and knee joints showed evidences of injury, but the chest did not. Results of physical examination were otherwise unimportant. The temperature rose to 38.5 C.; the pulse maintained a rate of 160 to 170. Rigidity and tenderness of the upper part of the abdomen led to laparotomy on the second day; nothing was found. On the third day pain, radiating to the left shoulder, first appeared; what seemed to be rapidly advancing pneumonia developed, and he died that day.

Pertinent necropsy findings were contusion of the left pectoral muscle and rupture of the pericardium on the left side with extrusion of the heart. The tear extended to within 3 cm. of the apex of the heart, and over the pericardial surfaces fibrin had been deposited. There was no blood staining of the pericardium. Congenital absence of the membrane was excluded by dissections demonstrating a normal course of the phrenic nerve. There was no mention of fractures of the sternum or ribs. Spitzmüller reasoned that rupture of the pericardium had been brought about by indirect trauma. In so doing he apparently overlooked the evidence of injury to the left pectoral muscle.

COMMENT

Since the publication of the first account of traumatic rupture of the pericardium, in 1706, this has been a well recognized type of injury. Even so, but little attention has been given the matter, as evidenced by the few and widely scattered references in the literature over a period of more than two hundred years. In this connection it is interesting to note the changing nature of the causative agents: Formerly the victims were struck by wagon tongues, run over by wagons or kicked by horses; at present, keeping pace with the machine age, the great majority are killed by automobiles.

From the standpoint of symptomatology the literature offers two points worthy of consideration. Both Allan [13] and Spitzmüller [1] mentioned the intense precordial pain, temporary in the first instance and constant in the second. Doughty's patient, although lacking angina, had marked cardiac embarrassment, which, however, could have been due in part to the diaphragmatic hernia. Our case is somewhat like Allan's, in that pain was present for a time and later disappeared. On the other hand, according to Kosmin,[24] an isolated wound of the pericardium not involving the blood vessels may be practically asymptomatic, because the pericardium as such does not give rise to pain and an injury to it need not necessarily be associated with a change in cardiac activity. Like Doughty's subject, ours died suddenly after a latent period, although from a different cause than his. A second observation, appar-

24. Kosmin, V. P.: Mechanism of the Origin and Differential Diagnosis of Wounds of the Pericardium Without injury to the Heart, Novy khir. arkhiv **32**:129, 1934.

ently long overlooked but of diagnostic importance, is the "water wheel murmur" heard and described by Lavallée in 2 proved instances of traumatic pericardial rupture. In the presence of such a sound the differential diagnosis lies between a traumatically produced pericardiopleural communication and pneumohydropericardium.

Although not proved by necropsy, the case reported by William Stokes [26] was probably an example of pericardial rupture. Clinically, the report was splendidly prepared, and for this and the further reason that the original is not readily accessible, we feel justified in summarizing the paper:

Mr. B., aged 21, had been in good health until 1822 (nine years before), when, while playing in a large water wheel, he was thrown on his face by the revolving wheel and caught half in and half out of the wheel in a line running from the inferior angle of the left scapula to the top of the right shoulder. With the next turn of the wheel he fell into the water, was rescued immediately and remained unconscious for three hours. On examination two lower ribs on the left side, the right clavicle, the humerus and the fifth to seventh ribs on the right side proved to be fractured. The right side of the face and thorax were emphysematous. There was complete paralysis of the right arm, with some loss of sensation. Subjectively there was great pain in the right side of the chest, giving the sensation of a foreign body which prevented respiration into the right lung. The pain was accompanied by a violent throbbing and heaving, and it was soon discovered that the heart was pulsating at the right side of the sternum. There was a short, dry cough but no hemoptysis.

Treatment consisted of bleeding and other measures. In two days the emphysema subsided. For the next month he was in bed, still suffering from a dry cough and pain in the side. The following month he was ambulatory. For the next eighteen months he experienced frequent recurrences of pain, which were invariably treated with the lancet. The function of the paralyzed arm gradually returned. The heart continued to pulsate on the right side, and the cough persisted, being aggravated by winter weather and by exercise. During several winters there were attacks of an "inflammatory nature" in which he suffered from violent pain in the right side of the chest, palpitation and marked dyspnea. These were always relieved by bleeding (about fifty times) without syncope, even when 30 ounces (890 cc.) of blood was taken. In 1829 he began taking digitalis, with considerable relief, and gradually increased the dose to 6 to 8 grains (0.39 to 0.5 Gm.) of the powder at a single dose, without untoward symptoms or a decrease of the pulse rate below 80. When first examined by Stokes the man was free from symptoms and appeared to be in good health. There was depression of the right shoulder; an increase of about an inch (2.5 cm.) in size was noted in the lower right side of the chest; the left side sounded clear; respirations were of the puerile type, and the sounds could be heard over the normal cardiac region, the sounds of the heart being imperceptible over the lower part of the chest and barely audible superiorly. The upper portion of the right lung was clear to the level of the fifth rib, but from there to the base it was completely dull. The

25. Footnote deleted.

26. Stokes, W.: A Case of Probable Dislocation of the Heart from External Violence, Edinburgh M. & S. J. **36**:45, 1931; London M. Gaz. **8**:560, 1831.

cardiac pulsation could be seen and felt in the right mammary region between the sixth and seventh ribs within an inch of the sternum. There were no signs of valvular disease.

Stokes said he felt that only traumatic rupture of the pericardium with displacement of the heart could account for the findings. His differential diagnosis included consideration of congenital malposition, extensive left pneumothorax, tumor of the left side of the thoracic cavity, extensive empyema, emphysema, herniation of viscera through the diaphragm and aneurysm of the abdominal aorta. In support of the diagnosis of traumatic pericardial rupture he stressed the insistence of the patient that previous to the accident he had often felt his heart pulsating in the normal position and was the first to point out to friends that the pulsation had shifted to the right side of the sternum after the accident. This ruled out the probability of congenital malposition of the heart. The finding of resonance and breath tones by percussion and auscultation satisfied Stokes that pneumothorax or tumor was not present. He employed the same argument against diaphragmatic hernia and in summarizing stated:

We must admit then that this is an example of dislocation of the heart with rupture of the pericardium and right pleura; a supposition which appears to me to agree perfectly with the history of the case and the state of the patient. . . From the history it appears probable that the patient has suffered repeated attacks of pleuritic inflammation of the right lung. . . But the most singular circumstance connected with this extraordinary case is the fact that the patient after so dreadful an accident, lived so long and enjoyed a tolerable state of existence.

If one could only be certain that a ruptured pericardium was responsible for the signs and symptoms, this case would be the most remarkable of its kind on record. To us it appears that diaphragmatic hernia was not adequately ruled out.

Another equivocal case is that described by Cameron:[27]

A man 67 years of age died of bronchopneumonia and dilatation of the heart without any physical signs pointing to the existence of the extensive pericardial defect discovered at necropsy. Five years before death the man had fallen a distance of 17 feet (5 meters) through a hatchway, sustaining numerous and serious injuries that rendered him unable to perform physical work thereafter. Positive necropsy evidences of the accident were sharp kyphosis of the spine at the level of the eleventh and twelfth thoracic vertebrae, with compensatory lordosis at the sixth dorsal body, severe right lateral scoliosis, absolute rigidity of the spine from the fifth dorsal vertebra caudally, deformities of the ribs resulting from the curvatures of the spine and a long scar in the right lobe of the liver anteriorly, with adhesion to the abdominal wall. Between the sternum and the pericardium were dense fibrous adhesions. The parietal pericardium was represented by only a pouchlike structure on the right and inferior aspect of the heart;

27. Cameron, A. L.: Defects of the Parietal Pericardium, Tr. Chicago Path. Soc. **9**:148, 1914.

the left side of the organ was entirely devoid of pericardial covering. The sac was about one-half the size of the heart and of sufficient size to accommodate the right auricle and about half of the ventricle. It resembled closely a normal pericardium through which a section had been made passing just to the left of the pulmonary artery and missing its attachments to the diaphragm on the left side by a distance of about 2 cm., the plane of the section being at right angles to the vertical plane of the body. Posteriorly the pericardium was represented by a narrow band of tissue 2 cm. at its greatest width and becoming narrowed as it ascended until it was cordlike and measured about 0.5 cm. at the junction with the pulmonary artery. The free left margin of the pouch was sharply defined except for a distance of about 7 cm. on the left inferior margin, where a flap of thin fibrous tissue, heavily laden with fat, was prolonged and lay free on the diaphragm. Inferiorly and posteriorly this flap was continuous with the pericardial sac. The fibrous pericardium was normal, save for several marked prolongations of fat-filled fibrous tissue which were present on its anterior aspect. The serous lining of the pouch was normal throughout.

Cameron reviewed only the literature on congenital pericardial defects. In the discussion he mentioned that the fall, with positive evidences of injury still remaining at the time of death, may have caused the heart to rupture through a comparatively normal pericardium. He likewise considered the possibility of a lesion partly congenital and partly traumatic, with enlargement of a congenital opening due to trauma. In conclusion he stated that the lack of other adhesions, and especially the free, rounded, fatty margin of the remaining pericardial folds, made it impossible to conclude that the defect was not congenital. There was no mention of the location or state of the phrenic nerves, so that this cannot be employed as evidence for or against either type of defect. The reader will not fail to see certain points of similarity between this case and our extraordinary one. If trauma was the cause of the pericardial lesion, Cameron's case is even more remarkable than ours with respect to the period of survival.

A point of parallelism between Allan's case and ours is the well defined retraction of the divided pericardium. Morel-Lavallée, Martin and Mazel, Doughty, Spitzmüller and possibly Reynier made similar observations. Any one who has seen Beck's [28] excellent motion pictures taken during operations on the heart can readily understand the mechanism of pericardial retraction and cardiac extrusion, for the movements and contortions of the heart held in restraint are most vigorous and it requires no imagination to visualize how such an organ may easily work its way through even a comparatively small opening in the pericardium and even bring about the purse string effect we have described.

28. Beck, C. S.: Noble Wiley Jones Lectures of the University of Oregon Medical School, 1937.

The fact that a number of patients have survived pericardial rupture for an appreciable time confirms the already well known fact that the pericardium is not an indispensible structure. While in certain of the cases on record pericarditis was present, this has been clearly related to trauma and hemorrhage and not to pulmonary infection. According to Southworth and Stevenson,[29] the spread of infection from the lungs or pleura to the exposed epicardium is the greatest single menace to the person with a congenitally defective pericardium. Our youngest subject escaped this complication either because of not having pneumonia between the date of the accident and the date of death or because the heart was not laid bare by retraction of the pericardium.

Lavallée appears to have been the first to attempt to explain the mechanics of pericardial rupture. It was his belief that when the heart and lungs are crushed against the vertebral column during an impact, tearing of the pericardium is produced by shearing or rubbing of the membrane against the bone. Later Lavallée, in discussing another case, stated that rupture might be produced by vibration, but again mentioned friction as a possibility.

Much later Spitzmüller postulated that force applied to the body, even if not directly on the chest, might be transmitted and produce a pendulum-like swing of the heart of sufficient magnitude so that the impact of the organ against the pericardium might cause it to rupture. It appears to us that an essential part of such a concept is the unwarranted assumption that the left border of the pericardium is weaker than other parts of it.

Certain facts demonstrated by our own series of cases of pericardial rupture as well as many of those reported in the literature are opposed to Spitzmüller's theory. First, it is hard to conceive of the possibility of any long sweeping motion of a structure so well stabilized against appreciable lateral motion by the short caval and pulmonary veins as the heart without laceration or actual rupture of one or more of these structures. While some of our patients displayed injury to the intrapericardial veins, we have not found it in the absence of fracture of the ribs in locations where damage by them offered the best explanation for injury of the vessels. In such cases we have ascribed the pericardial rupture to the same cause. Second, it is difficult to imagine that the heart, moving for such a short distance as it would within a previously normal pericardial sac, could attain enough momentum to rupture a relatively strong and fibrous sheath like the pericardium. Third, this theory fails to explain the relatively frequent rupture of the right side of the pericardium or of the anterior or posterior aspect. Fourth, Spitzmüller failed to take into account the almost constantly present

29. Southworth, H., and Stevenson, C. S.: Congenital Defects of the Pericardium, Arch. Int. Med. **61**:223 (Feb.) 1938.

evidences of injury to ribs or the thoracic wall in situations indicating that the impact was in an anteroposterior direction, wherein a pendulum motion of the heart could scarcely be imagined. Finally, in Spitzmüller's own subject there was hematoma beneath the pectoralis muscle, plainly indicating that trauma was applied directly to the chest and not, as he seems to have believed, indirectly in such a manner that the heart swung laterally in pendulum fashion with sufficient force to tear the sac about it.

With only slight modification it appears to us that the concept originally stated by Lavallée and so convincingly proved by Beck [30] as operating in traumatic rupture of the heart itself will also apply to the pericardium. Even in the absence of perforation or laceration of the pericardium due to fracture of the sternum or ribs, the following chain of events might logically be expected: 1. Forcible compression of the thorax occurs with at least momentary springing of the ribs and resultant deformity of the bony cage. 2. At the moment of maximum intensity of the externally applied force and its resultant compression, the heart may be caught between the anterior thoracic wall and the spine posteriorly, as Lavallée and Beck have shown. We feel, however, that instead of rubbing or shearing the pericardium, as Lavallée suggested, although this may be the mechanism at times, it is more likely that if the point of maximum intensity is broad enough, the result may be complete closure of the pericardial space at one point. If this happens to be over the heart itself, the organ within the closed-off portion of the sac may act as a fluid mass under tension and with the rapidly encroaching pressure may produce a relatively high internal expanding force within a fibrous membrane generally admitted to be inelastic when quickly stretched. These are essentially the conditions existing in a bag filled with water and squeezed from the top. At some point the pressure thus applied is sufficient to rupture the fabric. It is also comparable to the manner in which rupture or herniation of the sheath of the biceps brachialis muscle takes place. The site of pericardial rupture depends on several factors, e. g., the greatest free area or surface on which the expanding pressure is exerted, the direction of the applied force (the point where the sac is closed off), the direction from which the force is applied and, finally, the side of the spine to which the heart is shifted or slides when it is compressed. Thus, if the force is directed to the right anterolateral aspect of the chest, the heart would tend to be caught on the right side of the vertebral column, and the hydrostatic pressure would be exerted on its right border; if rupture took place, it would be there. In a similar manner, rupture of the left side of the organ could be brought about. The greater frequency of tears on the left side of the pericardium may be due to the fact that this is the largest free area and in this way possibly a site of weakness. The concept

30. Beck, C. S.: Contusions of the Heart, J. A. M. A. **104**:109 (Jan. 12) 1935.

advanced will also explain the reason why most ruptures occur on the side corresponding to the point of applied force.

We are acutely aware of the role of fracture of the ribs or sternum in the production of wounds of the pericardium and apply this hypothesis only to those instances in which there are no concomitant fractures, to ruptures of the pericardium in places where penetration by the ends of the ribs could not explain the rupture or to tears which are not of the puncture type and not associated with wounds of the myocardium. Such instances, especially in immediately fatal injuries, are by no means infrequent. The patients in our series who displayed tearing of the inferior vena cava, a finding that in our opinion would almost of necessity accompany the "pendulum swing" of the heart postulated by Spitzmüller as a cause of pericardial laceration, showed fractured ribs in situations that would readily explain the damage sustained by the vena cava.

An apparent exception to the rule that direct trauma of the chest may cause pericardial rupture is Kellert's [21] case, concerning which he offers two possible explanations:

> . . . first, that the weight of the falling earth, which being soft and adaptable, caused equal pressure over the chest resulting in great compression and bursting of the heart, very much as though a rubber bag distended with fluid were compressed at its middle. To obtain such an effect without fracture of the sternum or ribs seems very unlikely. The second and more probable explanation is that of hydraulic pressure. The large quantity of sandy soil exerted such great pressure over the lower half of the body as to drive most of the blood out of the vessels. This produced sudden over-distention of the heart, which was probably dilated as a result of physical exertion, with consequent rupture at several points. That the force was a great one is indicated by the ruptured pericardium and hemorrhages in the lung.

Despite every effort to discover all previous reports of pericardial rupture it is likely that some ruptures, particularly in association with traumatic rupture of the heart and not indicated in the titles, have been overlooked.

SUMMARY

Traumatic rupture of the pericardium is not, as the literature indicates, a rare occurrence. It is no doubt encountered as frequently in every series of autopsies on persons dying as a result of trauma as it has been in our series.

Commonly, pericardial rupture is merely one of many injuries and in most instances contributes little or nothing to the cause of death. One may rightly anticipate therefore that few examples of long survival will ever be recorded.

The pertinent data in 22 cases found among 4,107 consecutive and unselected cases studied at autopsy have been tabulated and evaluated. Among these, 1 case stands out conspicuously, not only in our group

but among all others on record, because of the fact that the child survived for two and one-half years and, further, because of the singular mechanism responsible for the sudden death. This case is described in detail.

The views of others and ourselves as to the mechanical principles involved in the production of pericardial rupture are given.

Since previous writers, other than Fischer (1868) and Schuster (1880), have not done so, we have attempted to collect and abstract all the literature on the subject. The majority of the earlier reports were available to us only through the articles by Fischer and Schuster. Including our 22 examples, the total number of reported cases now stands at 80.

NOTE.—Since the acceptance of the present study there has come to our attention the monograph by Erik Warburg, entitled "Subacute and Chronic Pericardial and Myocardial Lesions Due to Nonpenetrating Traumatic Injuries: A Clinical Study" (translated by H. Andersen and G. Seidelin, London, Oxford University Press, 1938).

A careful check of the text and bibliography of this excellent work fails to disclose additional instances of pericardial rupture.

Of interest in connection with our singular case is Warburg's statement that even sudden and surprising death occurring a long time after the trauma may be of traumatic origin (page 89).

EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

XIII. A SUMMARY OF THE EFFECT OF WHOLE LIVER, WHOLE MEAT, EXTRACTED LIVER AND EXTRACTED MEAT DIETS ON RENAL HYPERTROPHY, RENAL FUNCTION, BLOOD PRESSURE AND CARDIAC HYPERTROPHY

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The effect of diet on the function of the normal and the abnormal kidney has not been agreed on by experimental workers or clinicians. Reports from this laboratory have shown that renal hypertrophy, renal function, cardiac hypertrophy and blood pressure in intact and in partially nephrectomized rats are affected by diets containing varying concentrations of whole meat, extracted meat, whole liver and extracted liver. The purpose of this paper is to present a summary and comparison of these results obtained with the various diets.[1]

The experimental methods and the results have been presented in detail.[2] The whole and the water-extracted meat and liver were dried and incorporated in balanced experimental diets. All animals chosen

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1. The diets are abbreviated as follows: whole meat, M; extracted meat, EM; whole liver, L, and extracted liver, EL; the numbers following these letters designate the percentage concentration of the respective materials in the diet. The $\frac{\text{heart weight}}{\text{surface area}} \times 100$, $\frac{\text{kidney weight}}{\text{surface area}} \times 100$, $\frac{\text{liver weight}}{\text{surface area}} \times 100$ represent the weight of tissue per hundred square centimeters of surface area and are designated as $\frac{\text{H. W.}}{\text{S. A.}}$, $\frac{\text{K. W.}}{\text{S. A.}}$ and $\frac{\text{L. W.}}{\text{S. A.}}$, respectively. The percentage of nitrogen in the respective diets is shown in table 1.

2. (*a*) Chanutin, A., and Ferris, E. B., Jr.: Experimental Renal Insufficiency Produced by Partial Nephrectomy: I. Control Diets, Arch. Int. Med. **49**:767 (May) 1932. (*b*) Chanutin, A.: III. Diets Containing Whole Dried Liver, Liver Residue and Liver Extract, ibid. **54**:720 (Nov.) 1934; (*c*) V. Diets Containing Whole Dried Meat, ibid. **58**:60 (July) 1936. (*d*) Chanutin, A., and Ludewig, S.: XI. Diets Containing Dried Extracted Liver, ibid. **64**:513 (Sept.) 1939; (*e*) XII. Diets Containing Dried Extracted Meat, ibid. **64**:526 (Sept.) 1939.

for these analyses were fed the experimental diets from a minimum of seventy-five to a maximum of one hundred and seventy-five days.

KIDNEY WEIGHT

Intact Animals.—The average kidney weight per hundred square centimeters of surface area for intact rats is presented in table 2. It is seen that the $\frac{\text{K. W.}}{\text{S. A.}}$ ratios for the rats fed the whole meat diets tend to be smaller than those for rats on the remaining diets at the respec-

TABLE 1.—*Percentage of Nitrogen Content in the Rations*

Diet	Nitrogen	Diet	Nitrogen	Diet	Nitrogen	Diet	Nitrogen
M 10	1.7	EM 10	1.9	L 10	1.4	EL 10	1.5
M 20	2.8	EM 20	3.1	L 20	2.2	EL 20	2.9
M 40	5.2	EM 40	5.5	L 40	4.4	EL 40	5.1
.....	...	EM 60	8.4	L 60	6.2	EL 60	7.2
M 80	10.0	EM 80	11.1	L 80	8.2	EL 80	9.6

TABLE 2.—*The Effect of Diet on the Kidney Weight per Hundred Square Centimeters of Surface Area of Intact and of Partially Nephrectomized Rats* *

Protein Component, %	Average Kidney Weight, Mg.			
	Diet M	Diet EM	Diet L	Diet EL
Intact Rats				
10	358 (1.0)	416 (1.0)	362 (1.0)	390 (1.0)
20	426 (1.19)	441 (1.06)	388 (1.07)	413 (1.06)
40	442 (1.23)	491 (1.18)	495 (1.37)	450 (1.15)
60	.....	525 (1.26)	496 (1.38)	520 (1.33)
80	500 (1.40)	625 (1.50)	604 (1.67)	535 (1.37)
Partially Nephrectomized Rats				
10	182 (1.00)	229 (1.00)	166 (1.00)	222 (1.00)
20	245 (1.35)	311 (1.36)	266 (1.60)	304 (1.37)
40	318 (1.68)	385 (1.68)	438 (2.64)	388 (1.75)
60	.....	433 (1.89)	459 (2.76)	510 (2.30)
80	410 (2.26)	547 (2.39)	537 (3.24)	532 (2.40)

* The figures in parentheses represent the relative increases in kidney weight when the 10 per cent protein component is considered as 1.0.

tive levels of protein ingestion. It is also seen that there is a progressive increase in the size of all kidneys with increasing concentration of protein, but that the kidney weight per unit of the protein component is different for each dietary group. An analysis of renal hypertrophy on the basis of the nitrogen content of the diet yields similar results. Since the total solids of the kidneys of intact animals are found to be constant, the hypertrophy changes represent increases in kidney tissue.

Partially Nephrectomized Animals.—The values in table 2 for the partially nephrectomized rats show a progressive increase in the wet weight of the kidney stumps per unit of surface area with increasing

increments of protein in the diet. These values are not representative of true renal hypertrophy, owing to the wide variation in water content. The dried kidney weights available for the animals fed the EM and the EL diet, however, indicate that the proportionate increases in the $\frac{K.\ W.}{S.\ A.}$ ratios for the wet kidney weights are approximately correct. It is noted that the greatest range in values was obtained for the animals fed the whole liver diets.

If the average $\frac{K.\ W.}{S.\ A.}$ ratios for the intact and for the partially nephrectomized rats on the diets containing 10 per cent protein is considered as 1, the comparative increases in renal hypertrophy can be obtained. It is seen that the ratios for animals fed the M, the EM and the EL diet are quite similar. This is surprising in view of the rather wide differences in the absolute values of the respective $\frac{K.\ W.}{S.\ A.}$ ratios. Since there is a comparatively marked increase in the ratios of the animals fed whole liver diets, it follows that increasing amounts of water-soluble liver extractives affect the degree of renal hypertrophy markedly. It is difficult to estimate by either morphologic or functional studies how much of the hypertrophic substance in the kidney stump is due to inactive connective or degenerated tissue.

RENAL FUNCTION

Concentration Test.—Intact Animals: The urinary volumes and specific gravities of the intact animals were not affected by the different diets. Low urinary volumes and high specific gravities were obtained consistently.

Partially Nephrectomized Animals: The average values for urinary volumes, specific gravities and proteinuria for the rats fed the M, the EM and the L diet are summarized in table 3. These average values are presented to show the general trend of the effects of diets, although the individual variations are too large to attempt a statistical analysis. In general, a maximum increase in urinary volume and proteinuria and a maximum decrease for specific gravity was reached with each diet when the concentration of the protein component reached 40 per cent. The more concentrated protein diets caused negligible additional changes.

Urea Ratio.—Intact Animals: The average values for the urea ratio $\left(\frac{\text{urea excreted per hour}}{\text{urea in 100 cc. blood}} \times 100\right)$ of intact rats on the whole meat, the extracted meat and the extracted liver diets are summarized in table 4. There is a progressive increase in the values for the urea ratios with an increase in the amount of protein ingested with the exception of those for the group fed the EL 80 diet. The low value for this group may indicate renal damage. Furthermore, the urea ratios at the

respective levels of protein ingestion are quite similar, indicating that the type of protein is not an important factor in determining the degree of clearance.

The urea clearance per gram of kidney is given by the $\frac{\text{urea ratio}}{\text{kidney weight}}$ ratio and thus eliminates the factor of renal hypertrophy. The average values for these ratios are unusually constant for practically all diets

TABLE 3.—*Effect of Diet on the Average Values of Urinary Volume, Specific Gravity and Protein Excretion During a Concentration Test on Intact and on Partially Nephrectomized Rats*

Protein Component, %	Diet M	Diet EM	Diet L
	Volume of Urine (Cc.)		
10	4.6 (2.6)	5.8 (1.9)	3.5 (1.4)
20	8.0 (2.7)	9.5 (3.1)	6.5 (2.9)
40	12.4 (3.1)	13.5 (2.0)	13.3 (3.1)
60	.....	11.3 (2.6)	11.0 (2.4)
80	11.7 (2.6)	10.7 (2.8)	12.5 (2.6)
	Specific Gravity (Corrected)		
10	1.0280 (1.0433)	1.0289 (1.0500)	1.0340 (1.0496)
20	1.0247 (1.0490)	1.0242 (1.0480)	1.0326 (1.0532)
40	1.0207 (1.0513)	1.0197 (1.0601)	1.0207 (1.0524)
60	.....	1.0210 (1.0598)	1.0243 (1.0522)
80	1.0209 (1.0516)	1.0207 (1.0501)	1.0211 (1.0561)
	Urinary Protein (Mg.)		
10	29	53	15
20	83	96	116
40	133	111	128
60	...	103	119
80	142	99	74

* The figures in parentheses represent average values for intact rats.

TABLE 4.—*Effect of Diet on the Average Values of the Urea Ratios in Intact Rats*

Protein Component, %	Diet M	Diet EM	Diet EL
10	50	47	44
20	60	58	55
40	62	60	60
60	..	64	68
80	66	71	58

(table 5). It is seen that 11 of the 14 average values are within a range of 36 to 38. The values for the animals fed the EL 80 and the EM 80 diets are lower.

It has been demonstrated that renal hypertrophy and the urea ratio are generally increased following the ingestion of diets high in protein. The direct relation between the size of the kidneys and their function in the intact animal is demonstrated by the constancy of the $\frac{\text{urea ratio}}{\text{kidney weight}}$ ratio. This is a rather remarkable finding in view of the wide variety of diets fed these animals. There is no direct evidence available for explaining the low ratios obtained for the animals receiving the EM 80

and the EL 80 diet. In view of the facts presented, it must be assumed that an increase in renal activity due to excretion of metabolites is accompanied by an increase in the size of the kidneys and in renal function in the intact animals. These changes, however, do not affect the volume or the specific gravity of the urine collected during a concentration test.

Partially Nephrectomized Animals: The percentage incidence of the urea ratio values at different levels is presented in table 6. Ratios about 30 are considered to be within the normal range, and renal insufficiency becomes progressively greater with the lower ratios. It

TABLE 5.—*Effect of Diet on the Average Values of the* $\frac{\text{Urea Ratio}}{\text{Kidney Weight}}$ *Ratios in Intact Rats*

Protein Component, %	Diet M	Diet EM	Diet EL
10	36	36	39
20	37	37	38
40	36	37	38
60	..	37	38
80	38	32	33

TABLE 6.—*Effect of Diet on the Percentage Distribution of the Urea Ratios of Partially Nephrectomized Rats*

	Urea Ratio Range											
	Above 30 Diet			30-15 Diet			15-5 Diet			5-0 Diet		
Protein Components, %	M	EM	EL	M	EM	EL	M	EM	EL	M	EM	EL
10	3	2	0	58	43	21	39	49	76	0	6	3
20	0	0	0	42	21	43	55	71	48	3	8	9
40	0	0	0	11	11	25	68	70	63	21	19	12
60	..	0	0	..	30	34	..	60	59	..	10	7
80	0	2	0	27	29	52	60	69	42	13	0	6

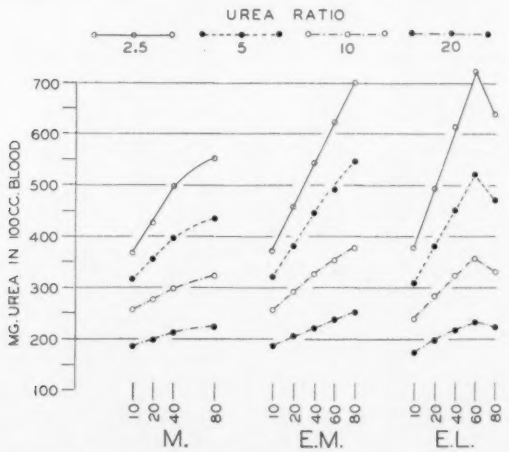
is seen that few partially nephrectomized animals have normal renal function. The greatest incidence of marked renal insufficiency, as judged by the percentage of animals with ratios below 15, was noted in the groups fed diets containing 40 per cent protein. The results of the concentration test appear to confirm the observations obtained with the urea clearance tests.

The accompanying chart illustrates the relation between the urea ratio and the concentrations of blood urea with the different diets. For a given urea ratio, the concentration of the blood urea is lowest for the group ingesting whole meat. The values are higher for the animals fed the extracted meat and the liver diets. They increase rapidly with an increase of protein content in the diet at any given ratio, except for an unexplained definite decrease in this relation in the group receiving the EL 80 diet.

BLOOD PRESSURE AND HEART WEIGHT

Intact Animals.—The blood pressures of the intact animals were quite constant, and the majority were between 120 and 130 mm. of mercury. The $\frac{\text{H. W.}}{\text{S. A.}}$ ratios were found to be variable, but the majority remained within a limited range.

Partially Nephrectomized Animals.—The effect of diet on the percentage distribution of blood pressures at selected levels is shown in table 7. The group of rats on the diets of extracted meat had the greatest incidence of hypertension (above 160 mm.). It is difficult to explain the difference between the animals on the M 10 and the



Relation between urea ratio and concentrations of blood urea.

EM 10 diet, since the incidence of hypertension was 14 and 52 per cent, respectively. The difference in these two diets is in the small amount of water-soluble extractives. It is striking that there is such a marked difference in the percentage incidence of hypertensive animals in the group fed the M and the EM diet and the groups fed the L and the EL diet at the 80 per cent protein level. The type and amount of protein in the diet unquestionably exerts a definite effect on blood pressure.

The correlation coefficients for the $\frac{\text{H. W.}}{\text{S. A.}}$ ratios and blood pressures are summarized in table 8. It is noted that the highest degree of correlation was uniformly obtained with diets containing 10 per cent protein. Of the values for the 19 diets, those for only 3 (EM 60, EM 80 and L 60) show a lack of correlation. A further analysis undertaken to determine the correlation coefficients for each diet gave

the following values: whole meat, 0.61 ± 0.034; extracted meat, 0.57 ± 0.020; whole liver, 0.67 ± 0.03, and extracted liver, 0.73 ± 0.02. These data demonstrate that there is a substantial or marked relation between the degree of hypertension and the degree of cardiac hypertrophy.

The Value of the $\frac{H.\ W.}{S.\ A.}$ per Unit of Blood Pressure.—In order to judge the efficiency of heart muscle, the milligrams of heart per hundred square centimeters of surface area were calculated for each 1.0 mm. of mercury blood pressure according to the formula $\frac{\text{H. W./S. A.}}{\text{blood pressure}}$

TABLE 7.—*Influence of Diet on the Percentage Distribution of the Blood Pressures at Different Levels*

	Blood Pressure Range											
	100-140 Mm. Diet				140-160 Mm. Diet				Above 160 Mm. Diet			
Protein Component, %	M	EM	L	EL	M	EM	L	EL	M	EM	L	EL
10	49	29	60	51	37	19	22	22	14	52	18	27
20	47	36	40	22	26	24	30	27	27	51	30	51
40	24	16	32	46	37	29	32	26	39	56	36	28
60	..	17	33	28	..	36	38	42	..	47	29	30
80	31	26	53	49	34	38	30	39	35	37	17	12

TABLE 8.—*Correlation Coefficients and Probable Errors Between $\frac{H.\ W.}{S.\ A.}$ Ratio and Blood Pressure of Partially Nephrectomized Rats*

EL 10.....0.76 ± 0.04	EM 10.....0.67 ± 0.05	M 10.....0.73 ± 0.049	L 10.....0.89 ± 0.029
EL 20.....0.49 ± 0.08	EM 20.....0.52 ± 0.06	M 20.....0.68 ± 0.056	L 20.....0.67 ± 0.083
EL 40.....0.59 ± 0.06	EM 40.....0.60 ± 0.06	M 40.....0.42 ± 0.085	L 40.....0.41 ± 0.11
EL 60.....0.44 ± 0.08	EM 60.....0.14 ± 0.10		L 60.....0.17 ± 0.11
EL 80.....0.49 ± 0.09	EM 80.....0.33 ± 0.07	M 80.....0.61 ± 0.086	L 80.....0.66 ± 0.105

The average data for the intact and for the partially nephrectomized rats are presented in table 9. It is evident that heart weights of both the intact and the partially nephrectomized rats were affected. Since the blood pressures of intact rats remained fairly constant regardless of diet, the differences in the heart weight per unit of blood pressure must be related to the dietary regimen. The average values for each group of animals were not affected by the concentration of protein fed. It is seen that the ratios for both the intact and the partially nephrectomized animals fed the EM and the EL diet are definitely smaller than those for the animals fed the M and the L diet. A statistical analysis was made to determine if there was a significant difference between the average values for intact and for partially nephrectomized rats on the same diet; positive differences were obtained for 13 of the 19 diets.

Despite the differences in the distribution of hypertensive animals in the various groups, hypertension appears to have practically no effect on the average ratios. Furthermore, a study of the ratios of individual animals indicates that the degree of hypertension does not necessarily determine the decreased values obtained for partially nephrectomized animals. It would seem that renal insufficiency per se influences the amount of cardiac tissue per unit of blood pressure.

SUMMARY

Diets containing protein components varying from 10 to 80 per cent of whole meat, extracted meat, whole liver and extracted liver, respectively, have been fed for periods of from seventy-five to one hundred and seventy-five days to intact and to partially nephrectomized rats. The effect of these diets on renal hypertrophy, renal function, blood pressure and cardiac hypertrophy has been studied with reference to the amount and type of the protein component in the diet.

In the intact rat each increment of the protein component generally caused a progressive renal hypertrophy and an increase in the urea clearance. Variations in the protein content did not affect the volume or specific gravity of the urine obtained during a concentration test with a twenty-four hour specimen. The blood pressures and the size of the hearts were not appreciably affected by augmenting the protein components. The main effect of the type of protein component was

TABLE 9.—*Influence of Diet on the Milligrams of Heart per Hundred Square Centimeters of Surface Area for each 1 Mm. of Blood Pressure*

Diet	Intact Rats	Partially Nephrectomized Rats
EM 10	1.29 ± 0.022	1.21 ± 0.020
EM 20	1.31 ± 0.020	1.21 ± 0.022
EM 40	1.27 ± 0.019	1.16 ± 0.018
EM 60	1.24 ± 0.018	1.11 ± 0.028
EM 80	1.31 ± 0.019	1.17 ± 0.017
Average	1.28	1.17
EL 10	1.27 ± 0.015	1.26 ± 0.023
EL 20	1.33 ± 0.019	1.27 ± 0.024
EL 40	1.34 ± 0.022	1.22 ± 0.018
EL 60	1.33 ± 0.018	1.19 ± 0.023
EL 80	1.26 ± 0.018	1.15 ± 0.022
Average	1.31	1.22
M 10	1.43 ± 0.045	1.34 ± 0.026
M 20	1.48 ± 0.031	1.33 ± 0.026
M 40	1.42 ± 0.036	1.27 ± 0.023
M 80	1.39 ± 0.033	1.29 ± 0.041
Average	1.43	1.31
L 10	1.45 ± 0.033	1.42 ± 0.027
L 20	1.60 ± 0.047	1.38 ± 0.037
L 40	1.58 ± 0.041	1.40 ± 0.043
L 60	1.59 ± 0.057	1.41 ± 0.044
L 80	1.50 ± 0.047	1.37 ± 0.033
Average	1.54	1.39

manifested by the larger amount of heart muscle per unit of surface area required to maintain a given blood pressure in the animals on the whole meat and the whole liver diets.

In the partially nephrectomized animals the effect of increasing the protein component of the diet on renal hypertrophy was similar to that in the intact animals. Urinary volumes, proteinuria, hyposthenuria and a decrease in urea clearance were progressive with protein increments of from 10 to 40 per cent, but further increments caused no further constant effect on the measure of renal function. The type of the protein component appeared to influence the incidence of hypertensive rats, particularly in the group fed the extracted meat diets. The values for the heart weight per unit of surface area for a given blood pressure were significantly smaller for the partially nephrectomized rats than for the intact rats on the same diet.

CONCLUSIONS

It appears from these experiments that the concentration of the protein in the diet has a greater effect on the function of the normal and the abnormal kidney than the type of the protein component.

EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

XIV. DIETS CONTAINING WHOLE DRIED YEAST

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Numerous workers [1] have reported that the administration of yeast extracts to white rats is effective in preventing renal hypertrophy caused by excessive ingestion of protein. There are no data showing the possible relation between the size and the function of the kidneys under such conditions. This investigation was undertaken to study the effect of feeding diets containing varying concentrations of dried yeast on renal hypertrophy, renal function and blood pressure in intact and in partially nephrectomized rats.

EXPERIMENTAL METHODS

The details of the procedures for the care of the animals and for determining the blood pressure and renal function have been presented in previous papers.[2] Eighty to 90 per cent of the total kidney tissue was removed by a two stage operation from the partially nephrectomized rats.

Five experimental diets were used and were designated as Y 20, Y 30, Y 40, Y 60 and Y 80 according to the percentage of dried yeast which they contained. The composition of the diets is shown in table 1. The experimental period lasted for about one hundred days with a maximum and minimum of one hundred and eight and ninety-five days, respectively.

The ratio of the weight of the heart and kidneys to surface area is expressed by $\frac{\text{H. W.}}{\text{S. A.}}$ and $\frac{\text{K. W.}}{\text{S. A.}}$, respectively. The surface area was calculated from the weight of the animal by the formula of Lee.[3]

The dried yeast was contributed by Standard Brands, Inc.

From the Laboratory of Physiological Chemistry, the University of Virginia.

This work was aided by a grant from the Penrose Fund of the American Philosophical Society.

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2. Chanutin, A., and Ludewig, S.: Experimental Renal Insufficiency Produced by Partial Nephrectomy: V. Diets Containing Whole Dried Meat, Arch. Int. Med. **58**:60 (July) 1936.

3. Lee, M. O.: Am. J. Physiol. **89**:24, 1929.

EXPERIMENTAL RESULTS AND ANALYSIS OF OBSERVATIONS

Controls.—A summary of results, including surface area, blood pressure, $\frac{\text{H. W.}}{\text{S. A.}}$ and $\frac{\text{K. W.}}{\text{S. A.}}$ ratios, total solids of the kidneys, urea ratio and $\frac{\text{urea ratio}}{\text{kidney weight}}$ ratio, respectively, for intact rats is presented in table 2.

The individual and mean values for blood pressure are greatest for the group receiving the Y 20 diet and least for the group receiving the Y 80 diet. The values for the rats receiving the Y 30, the Y 40 and the Y 60 diet are fairly constant. Of the 69 blood pressure values, 2 are above 150 mm. and 3 above 140 mm. of mercury. With these few exceptions, the yeast diets exerted no significant influence on the blood pressure of intact rats.

The $\frac{\text{H. W.}}{\text{S. A.}}$ ratios for the group fed the Y 20 diet are slightly greater than those for the remaining groups. The relation between blood

TABLE 1.—*Composition of Experimental Diets*

Diet	Concentration of Component in Diet, Percentage					
	Yeast	Starch	Lard	Cod Liver Oil	Salt Mixture*	Nitrogen Content
Y 20	20	54	17	5	4	1.9
Y 30	30	44	17	5	4	2.5
Y 40	40	34	17	5	4	3.3
Y 60	60	14	17	5	4	4.7
Y 80	80	5	6	5	4	6.6

* Osborne and Mendel.[2]

pressure and $\frac{\text{H. W.}}{\text{S. A.}}$ is extremely constant for all the control animals.

The mean values for $\frac{\text{K. W.}}{\text{S. A.}}$ ratios are constant for the rats fed the Y 20, the Y 30 and the Y 40 diet, which indicates failure of the kidneys to hypertrophy with increased ingestion of protein. There was, however, an appreciable renal hypertrophy in the animals fed the Y 60 and the Y 80 diet. These relations are presented more accurately in chart 1, in which the individual values of $\frac{\text{dry kidney weight}}{\text{surface area}}$ ratios are shown.

The individual values for the urea ratios vary markedly and depend on the kidney weight. This is shown by the constancy of the $\frac{\text{urea ratio}}{\text{kidney weight}}$ ratios, which average 36, 35, 41, 40 and 36 for the respective yeast diets, beginning with the Y 20.

Partially Nephrectomized Rats.—The effects of the Y 20, the Y 30, the Y 40 and the Y 60 diet on partially nephrectomized rats are shown

TABLE 2.—*Observations on Control Animals Fed a Variety of Diets*

Renal Condition and Diet	Value	Duration of Experiment, Days	Surface Area	Blood Pressure, Mm.	Heart Weight / Surface Area × 100	Kidney Weight / Surface Area × 100	Total Solids of the Kidneys, %	Urea Ratio	Urea Ratio / Kidney Weight
2 kidneys	Minimum	103	354	126	0.164	0.386	24.5	39	27
Y 20	Maximum	103	444	156	0.200	0.427	26.2	70	41
	Average	103	395	133 ± 3.33	0.178 ± 0.008	0.405 ± 0.004	25.1	57 ± 3.5	36
	Rats	9	9	9	9	9	9	9	9
2 kidneys	Minimum	96	308	114	0.132	0.361	24.2	42	25
Y 30	Maximum	118	480	134	0.183	0.465	26.5	88	44
	Average	105	404	125 ± 1.59	0.161 ± 0.003	0.415 ± 0.006	25.7	58 ± 4.7	35
	Rats	16	16	16	16	16	16	10	10
2 kidneys	Minimum	96	283	102	0.143	0.346	22.9	51	36
Y 40	Maximum	103	444	154	0.188	0.478	26.8	82	51
	Average	100	370	124 ± 2.74	0.165 ± 0.003	0.412 ± 0.009	25.2	66 ± 3.6	41
	Rats	17	17	17	17	17	9	9	9
2 kidneys	Minimum	98	345	112	0.151	0.409	23.8	49	31
Y 60	Maximum	99	430	142	0.171	0.550	26.9	99	50
	Average	99	384	127 ± 2.63	0.161 ± 0.005	0.473 ± 0.010	25.7	73 ± 3.87	40
	Rats	14	14	14	14	14	14	14	14
2 kidneys	Minimum	102	244	94	0.134	0.410	22.0	48	23
Y 80	Maximum	105	394	132	0.182	0.648	25.6	105	48
	Average	103	336	114 ± 2.9	0.162 ± 0.004	0.564 ± 0.020	23.9	70 ± 5.3	36
	Rats	13	13	13	13	13	13	10	10

in tables 3 to 6, respectively. Charts 2 to 6 were prepared from these tables to facilitate comparisons of the effect of different diets on the blood pressure, kidney weight and renal function. Owing to the lack of sufficient yeast, the Y 80 diet was not fed to the partially nephrectomized animals.

Blood Pressure: The outstanding effect on blood pressure was found to be the definite increase of hypertensive animals in the group receiving the Y 60 diet. The animals receiving the remaining diets showed only slight changes in the percentage distribution of blood pressures (chart 2).

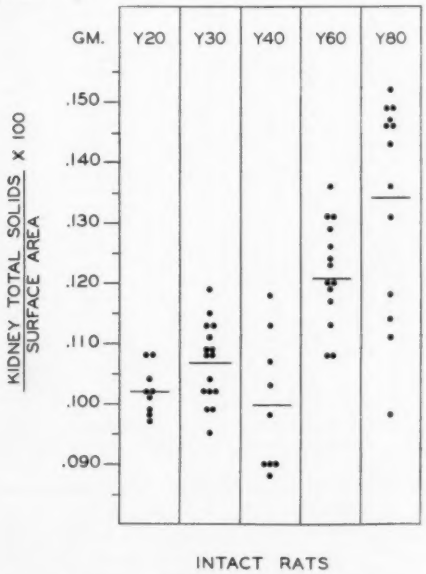

Chart 1.—Effect of diet on the solids of the kidneys per hundred square centimeters of surface area in intact rats.

It has been well established that there is a fairly substantial relation between the $\frac{\text{H. W.}}{\text{S. A.}}$ ratio and the height of blood pressure of partially nephrectomized rats. The correlation coefficients and probable errors as calculated for partially nephrectomized rats fed yeast diets follow: Y 20, 0.66 ± 0.058; Y 30, 0.46 ± 0.113; Y 40, 0.64 ± 0.072, and Y 60, 0.65 ± 0.076. These results indicate that there is a substantial or marked relation between cardiac hypertrophy and blood pressure.

Kidneys: The individual values for the $\frac{\text{dry kidney weight}}{\text{surface area}}$ ratios are presented in chart 3. There is a progressive increase in the mean weight of the dried kidneys per hundred square centimeters as follows: Y 20,

TABLE 3.—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 20 per Cent Dried Yeast*

Rat	Duration of Experiment, Days	Surface Area, Sq. Cm.	Blood Pressure, Mm.	Heart Weight / Surface Area × 100	Kidney Weight / Surface Area × 100	Total Solids of Kidneys, %	Urea Ratio
1	95	291	176	0.190	0.198	20.8	13
2	95	232	210	0.232	0.145	21.2	8
3	95	276	166	0.221	0.132	20.8	12
4	95	286	136	0.189	0.201	21.6	29
5	95	283	134	0.176	0.188	17.5	9
6	95	254	...	0.203	0.195	22.4	15
7	95	265	134	0.185	0.201	24.6	24
8	95	289	156	0.189	0.207	23.9	23
9	95	232	216	0.226	0.142	16.1	7
10	95	322	134	0.180	0.215	20.2	23
11	95	258	138	0.171	0.200	20.2	14
12	95	286	136	0.159	0.178	24.4	34
13	95	234	158	0.187	0.191	22.4	22
14	95	270	144	0.199	0.192	24.5	16
15	95	228	136	0.154	0.178	24.8	17
16	95	270	184	0.205	0.194	23.4	19
17	95	268	160	0.195	0.178	25.8	22
18	95	244	170	0.211	0.184	21.8	11
19	95	234	148	0.195	0.189	20.1	7
20	95	272	130	0.172	0.164	24.0	20
21	99	304	136	0.191	0.204	18.9	..
22	99	314	...	0.218	0.242	22.7	9
23	99	283	148	0.190	0.244	21.0	9
24	99	324	154	0.193	0.230	22.9	22
25	99	348	152	0.192	0.214	22.0	24
26	99	289	136	0.175	0.162	21.8	10
27	99	297	146	0.173	0.211	20.3	..
28	99	308	144	0.162	0.184	23.2	..
29	99	320	146	0.170	0.200	22.0	18
30	99	299	134	0.187	0.208	24.2	..
31	99	295	198	0.196	0.252	20.0	12
32	99	272	154	0.172	0.188	23.1	14
33	105	295	148	0.185	0.152	21.6	13
34	105	310	136	0.223	0.223	24.0	24
35	105	220	152	0.150	0.149	23.2	..
36	105	230	216	0.241	0.223	19.0	9
37	105	231	196	0.194	0.195	21.4	12
38	105	289	126	0.165	0.178	24.6	22
39	105	306	144	0.173	0.167	23.8	15
40	105	230	196	0.183	0.208	19.2	8
41	105	238	128	0.176	0.153	25.2	21
42	105	254	156	0.186	0.181	21.4	22
43	108	362	152	0.217	0.229	23.0	12
44	108	268	...	0.179	0.150	21.6	..

TABLE 4.—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 30 per Cent Dried Yeast*

Rat	Duration of Experiment, Days	Surface Area, Sq. Cm.	Blood Pressure, Mm.	Heart Weight / Surface Area × 100	Kidney Weight / Surface Area × 100	Total Solids of Kidneys, %	Urea Ratio
1	96	343	128	0.181	0.191	23.4	25
2	96	289	180	0.353	0.282	15.5	5
3	96	328	206	0.243	0.178	19.0	8
4	96	260	...	0.193	0.192	22.3	13
5	96	268	...	0.161	0.170	22.7	20
6	96	350	156	0.187	0.186	17.8	22
7	96	386	138	0.183	0.222	23.4	..
8	98	254	160	0.157	0.202	23.2	22
9	98	278	128	0.171	0.205	22.7	23
10	98	348	142	0.176	0.227	24.2	27
11	98	328	156	0.175	0.214	21.0	19
12	98	368	206	0.218	0.254	17.4	11
13	98	348	148	0.176	0.243	20.8	13
14	98	310	108	0.244	0.242	20.6	23
15	98	376	108	0.214	0.316	18.9	12
16	98	307	132	0.173	0.215	19.8	12
17	98	360	184	0.280	0.280	16.5	..
18	98	297	124	0.203	0.246	21.0	..
19	102	306	164	0.190	0.196	22.7	20
20	102	334	170	0.181	0.192	21.4	16
21	102	306	150	0.173	0.215	20 2	23
22	102	412	146	0.174	0.211	21.0	15
23	102	265	190	0.192	0.204	24.3	10

TABLE 5.—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 40 per Cent Dried Yeast*

Rat	Duration of Experiment, Days	Surface Area, Sq. Cm.	Blood Pressure, Mm.	Heart Weight / Surface Area × 100	Kidney Weight / Surface Area × 100	Total Solids of Kidneys, %	Urea Ratio
1	97	297	130	0.171	0.233	24.0	32
2	97	286	118	0.165	0.229	22.0	23
3	97	265	134	0.190	0.224	19.0	18
4	97	345	...	0.248	0.301	16.8	10
5	97	302	154	0.187	0.246	18.4	14
6	97	374	122	0.171	0.222	23.6	25
7	97	426	130	0.194	0.294	22.4	26
8	97	376	152	0.186	0.249	20.9	12
9	102	308	196	0.209	0.386	15.9	10
10	102	383	158	0.168	0.342	18.1	20
11	102	290	164	0.177	0.274	18.7	23
12	102	323	154	0.187	0.279	18.4	21
13	102	280	150	0.201	0.298	18.9	12
14	102	379	138	0.173	0.300	18.9	16
15	102	370	194	0.203	0.378	15.0	..
16	102	372	180	0.214	0.366	16.7	12
17	102	360	214	0.232	0.379	14.8	9
18	103	278	128	0.154	0.201	22.2	..
19	103	291	158	0.181	.....	....	..
20	103	274	...	0.153	0.232	22.6	..
21	103	265	114	0.153	0.231	21.4	..
22	103	280	130	0.148	0.208	23.2	..
23	103	265	154	0.164	0.208	22.7	..
24	103	272	152	0.178	0.237	20.5	..
25	103	297	156	0.177	0.249	21.8	34
26	107	339	156	0.216	0.322	16.5	..
27	107	...	...	.....	0.250	26.2	26
28	107	301	146	0.161	0.232	23.2	14
29	107	339	180	0.173	0.262	19.3	11
30	107	330	166	0.213	0.310	19.9	14
31	107	345	142	0.162	0.257	24.2	17
32	107	336	...	.....	0.247	18.7	..
33	107	354	160	0.224	0.266	16.9	6
34	107	310	174	0.200	0.202	22.4	5

TABLE 6.—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 60 per Cent Dried Yeast*

Rat	Duration of Experiment, Days	Surface Area, Sq. Cm.	Blood Pressure, Mm.	Heart Weight / Surface Area × 100	Kidney Weight / Surface Area × 100	Total Solids of Kidneys, %	Urea Ratio
1	97	308	144	0.187	0.304	22.0	10
2	97	307	156	0.181	0.354	18.2	12
3	97	292	176	0.216	0.292	17.5	10
4	97	295	176	0.207	0.315	16.4	11
5	97	341	176	0.212	0.440	16.4	15
6	97	334	140	0.183	0.382	16.9	10
7	97	307	...	0.191	0.478	14.3	9
8	97	316	174	0.181	0.247	16.0	..
9	97	308	214	0.226	0.367	15.9	10
10	97	302	206	0.218	0.335	14.9	15
11	97	348	126	0.163	0.314	20.7	9
12	97	328	160	0.174	0.326	17.2	17
13	97	291	212	0.236	0.339	12.7	5
14	97	320	186	0.201	0.507	13.4	9
15	97	299	148	0.253	0.321	16.4	..
16	104	318	166	0.198	0.320	19.2	13
17	104	322	210	0.276	0.288	15.3	11
18	104	316	178	0.218	0.340	15.5	9
19	104	324	180	0.202	0.328	17.4	12
20	104	306	162	0.200	0.325	16.2	9
21	104	356	186	0.225	0.446	15.0	9
22	104	280	166	0.234	0.354	18.7	6
23	104	360	132	0.183	0.302	17.5	18
24	104	240	...	0.196	0.312	20.0	20
25	104	250	210	0.231	0.485	12.4	9
26	104	330	142	0.160	0.352	20.2	13
27	104	339	146	0.183	0.304	17.1	11
28	104	339	138	0.177	0.294	20.3	15

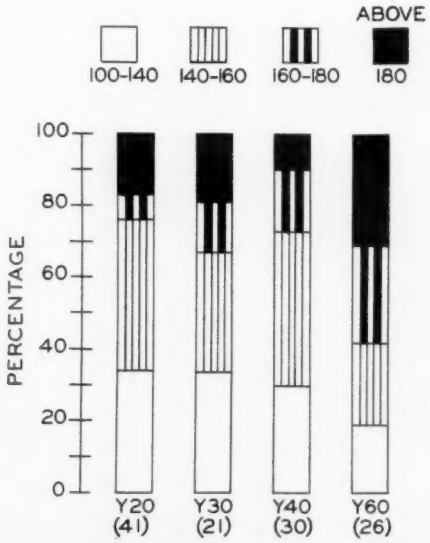

Chart 2.—Effect of diet on the blood pressure of partially nephrectomized rats. The figures in parentheses in this and in similar charts indicate the number of animals.

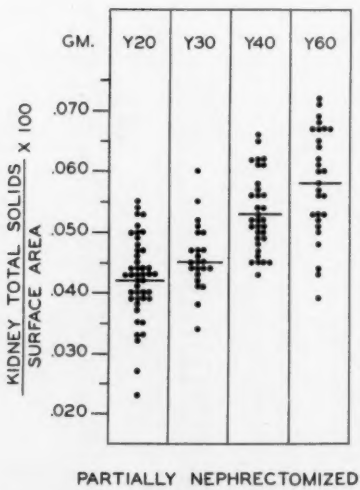

Chart 3.—Effect of diet on the solids of the kidneys per hundred square centimeters of surface area in partially nephrectomized rats.

42 mg.; Y 30, 45 mg.; Y 40, 53 mg., and Y 60, 58 mg. If the average value for the group fed the Y 20 diet is considered as 1, the ratios for the respective diets are 1.0, 1.07, 1.26 and 1.38. Apparently yeast does not prevent renal hypertrophy of the kidney remnant as it does for the intact kidneys.

Urea Ratio: The percentage distribution of urea ratios at different levels is shown in chart 4. The complete absence of ratios below 5 in this entire series is unusual and striking. There is little difference in the distribution of the ratios for the animals fed the Y 20, the Y 30 and the Y 40, but there is a definite increase in the ratios with values between 5 and 15.

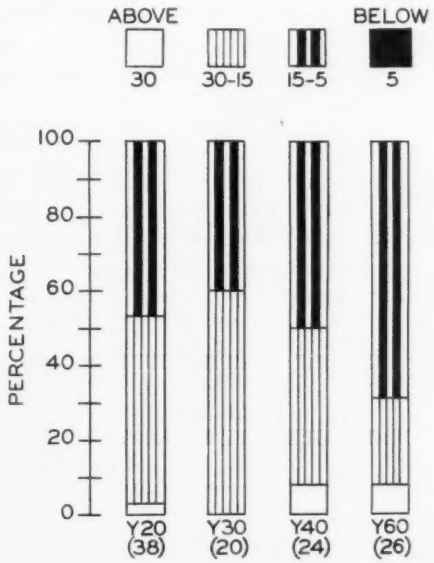

Chart 4.—Effect of diet on the urea ratio of partially nephrectomized rats.

The Effect of Diet on the Blood and Urine Urea.—The adjusted curves and their formulas, obtained by methods previously described, showing the effect of dried yeast diets on the amount of urea in the blood and the urine in relation to the urea ratio of control and experimental rats are shown in chart 5. It is seen that with progressively increased ingestion of yeast there is a greater increase in the concentration of blood urea and a proportionately smaller increase in the concentration of urine urea at any given urea ratio. These increased values represent retention of nitrogen and the inability to excrete administered urea properly.

The effect of diet on the concentration of blood urea at different urea ratios in percentage of mean normal is shown in chart 6. It is striking that there is only a comparatively small difference in the concentration of blood urea at a urea ratio as low as 5 for the different diets.

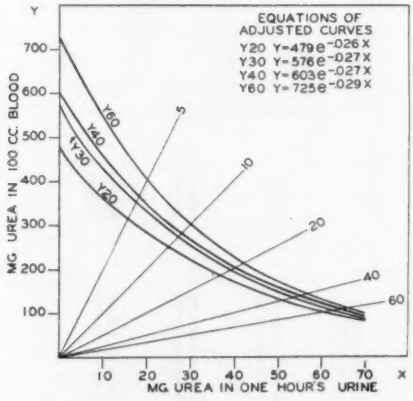

Chart 5.—Relation of the adjusted curves for blood urea and urine urea.

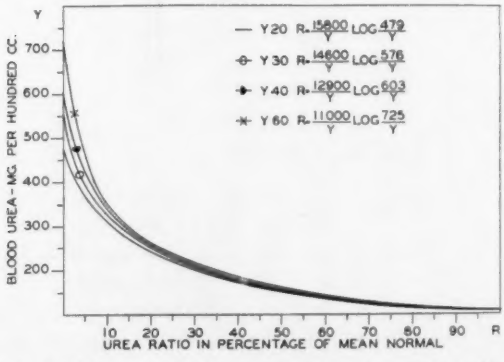

Chart 6.—Relation between the concentration of urea in the blood and the urea ratio in percentage of the mean normal value.

COMMENT

Longwell and his co-workers [1] have reviewed the effect of yeast concentrates on renal hypertrophy produced by diets high in protein (casein). There is general agreement that there is a prevention or inhibition of renal hypertrophy with these extracts, which appear to be

rich in the vitamin B complex. In the present experiment yeast served both as a source of protein and as the inhibiting factor concerned in renal hypertrophy. The results obtained confirm previous workers so far as preventing renal hypertrophy in intact animals with diets contaning comparatively small amounts of yeast.

The inhibiting factor must be considered in relation to the protein fed. Casein has been used by most investigators and is recognized as the least nephrotoxic protein for rats. Whole dried liver, which is rich in the vitamin complex, causes a progressive increase in the size of the kidney with increased concentration in the diet. When the yeast concentration of the diet increases markedly, there is no longer any inhibition in the size of the kidneys of intact rats. Since it has been demonstrated that diets rich in nucleic acid [4] and phosphates [5] may be nephrotoxic in the rat, it may be that these factors may be operative in counteracting the effect of the "inhibiting" factor.

In the partially nephrectomized rat, the total solids of the kidney stump increase progressively with increased ingestion of yeast. Since it is impossible to determine accurately the increase in connective tissue in these kidneys, one cannot judge the effect of the "inhibitory" substance on the functioning kidney units.

If the effect of yeast diets on the concentration of urea in the blood and the urine is taken as an index of renal function, it will be seen that there are no urea ratios below 5 for the entire series. This is unusual, since ratios of this magnitude and smaller are obtained for partially nephrectomized animals fed other diets. Furthermore, this is reflected in the relatively low concentrations of blood urea obtained at different urea ratios. If these results are accepted as indexes of renal function, diets containing yeast are relatively less nephrotoxic to rats than such foodstuffs as dried meat, liver, extracted meat or extracted liver.

SUMMARY

The effect of feeding diets containing various percentages of dried yeast to intact rats (20, 30, 40, 60 and 80 per cent) and to partially nephrectomized rats (20, 30, 40 and 60 per cent) has been studied.

Data showing the effects of these diets on renal hypertrophy, renal function and blood pressure in intact rats are presented. There was no change in the $\frac{\text{dry kidney weight}}{\text{surface area}}$ ratios for the animals ingesting the diets containing 20, 30 and 40 per cent yeast, but there was a relatively marked increase in the ratios for the animals receiving the Y 60 and the Y 80 diet, indicating that yeast contains substances capable of

4. Newburgh, L. H., and Johnston, M. W.: J. Clin Investigation **10**:153, 1931.
5. MacKay, E. M., and Oliver, J.: J. Exper. Med. **61**:319, 1935.

preventing hypertrophy within definite limits of protein intake. The $\frac{\text{urea ratio}}{\text{kidney weight}}$ ratios and the blood pressures were fairly constant with all diets.

The following observations were made on the partially nephrectomized rats:

There was a progressive increase in the $\frac{\text{dry kidney weight}}{\text{surface area}}$ ratios with increasing concentration of yeast in the diet. Yeast does not prevent renal hypertrophy of the kidney remnant.

The incidence of hypertension was greatest in the group ingesting the diet containing 60 per cent yeast.

There was no marked renal insufficiency in any of these animals, as judged by the urea ratios. Furthermore, the concentrations of blood urea were not markedly elevated at the lower urea ratios.

AGE, SEX AND HYPERTENSION IN MYOCARDIAL INFARCTION DUE TO CORONARY OCCLUSION

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For many years coronary occlusion was considered a disease of old age and emphasis was laid on the marked discrepancy in its incidence between the sexes. More recently, as the diagnosis of occlusion has become more precise, there has been an increasing number of reports of its occurrence in persons in the younger age groups and in women as well as men. Conner and Holt [1] and, later, Bean [2] took into consideration certain factors of age and sex in their discussion of the prognosis and course of the disease.

In view of the extreme importance of coronary occlusion, a large series of cases observed by us has been analyzed with a view to determining the influence of age, sex and hypertension on the incidence and prognosis of the disease as well as on its various clinical manifestations. In addition, particular attention has been paid to the relation of hypertension to age and sex.

MATERIAL

During the past five years, 500 cases of coronary occlusion were studied in the wards and private pavilion of the Mount Sinai Hospital. These were consecutive cases, included regardless of the type of treatment. Approximately 85 per cent of the patients were Jewish because of the predominance of this racial group in the hospital.

In the following analysis are included only cases in which a typical history, electrocardiogram or postmortem confirmation was present. The course of the disease in these cases was observed by us in great detail, both clinically and by laboratory methods.

From the Cardiographic Laboratory and the Medical Services of the Mount Sinai Hospital.

1. Conner, L. A., and Holt, E.: The Subsequent Course and Prognosis in Coronary Thrombosis, Am. Heart J. **5**:705, 1930.

2. Bean, W. B.: Infarction of the Heart: A Morphological and Clinical Appraisal of Three Hundred Cases, Am. Heart J. **14**:684, 1937.

OBSERVATIONS

Sex.—Of the 500 patients 387, or 77.4 per cent, were men and 112, or 22.6 per cent, were women, a ratio of 3.4:1 (table 1). This is lower than the calculated ratio of 4.6:1 in 2,803 clinical cases cited in the literature, representing a total of 14 series of cases.[3] The lowest ratio of men to women in the individual series was 3:1,[4] and the highest, 13:1.[3a] The ratio is somewhat lower in series of cases in which necropsy was performed; in 1,241 such cases[5] it was 3:1. Except for

3. (*a*) Parkinson, J., and Bedford, D. E.: Cardiac Infarction and Coronary Thrombosis, Lancet **1**:4, 1928. (*b*) Levine, S. A.: Coronary Thrombosis, Medicine **8**:245, 1929. (*c*) Bramwell, C.: Coronary Occlusion, Brit. M. J. **1**:681, 1930. (*d*) Harrington, A. W., and Wright, J. H.: Cardiac Infarction: A Study of One Hundred and Forty-Eight Cases, Glasgow M. J. **119**:1, 1930. (*e*) White, P. D., and Bland, E. F.: A Further Report on the Prognosis of Angina Pectoris and of Coronary Thrombosis: A Study of Five Hundred Cases of the Former Condition and of Two Hundred Cases of the Latter, Am. Heart J. **7**:1, 1931. (*f*) Allen, O. S.: Acute Coronary Thrombosis, Delaware State M. J. **6**:252, 1934. (*g*) Riesman, D., and Harris, S. E.: Disease of the Coronary Arteries with a Consideration of Data on the Increasing Mortality of Heart Disease, Am. J. M. Sc. **187**:1, 1934. (*h*) Howard, T.: Coronary Occlusion, M. Times & Long Island M. J. **62**:337, 1934. (*i*) Willius, F. A.: Life Expectancy in Coronary Thrombosis, J. A. M. A. **106**:1890 (May 30) 1936. (*j*) Vander Veer, J. B., and Brown, L. E., Jr.: The Diagnosis and Prognosis of Coronary Occlusion: The Electrocardiogram as an Aid, Pennsylvania M. J. **39**:303, 1936. (*k*) Landau, N., cited in Coronary Occlusion, Special Articles (Vienna), Lancet **1**:388, 1936. (*l*) Mullins, W. L.: Age Incidence and Mortality in Coronary Occlusion: A Review of Four Hundred Cases, Pennsylvania M. J. **39**:322, 1936. (*m*) Palmer, J. H.: The Blood Pressure in the Years Following Recovery from Coronary Thrombosis, Lancet **1**:741, 1937. Conner and Holt.[1]

4. Bramwell.[3c] Harrington and Wright.[3d] Mullins.[3l]

5. (*a*) Wearn, J. T.: Thrombosis of Coronary Arteries with Infarction of the Heart, Am. J. M. Sc. **165**:250, 1923. (*b*) Warburg, E. J.: Ueber den Coronarkreislauf und über die Thrombose einer Coronararterie: Anatomie, Physiologie und Historik, Acta med. Scandinav. **73**:425, 1930. (*c*) Klotz, O., and Lloyd, W.: Sclerosis and Occlusion of the Coronary Arteries, Tr. A. Am. Physicians **5**:08, 1930. (*d*) Covey, G. W.: Coronary Thrombosis: A Review of Autopsy Findings, Nebraska M. J. **15**:466, 1930. (*e*) Jervell, A.: Elektrokardiographische Befunde bei Herzinfarkt, Acta med. Scandinav., 1935, supp. 68, p. 1. (*f*) Lisa, J. R., and Ring, A.: Myocardial Infarction or Gross Fibrosis: Analysis of One Hundred Necropsies, Arch. Int. Med. **50**:131 (July) 1932. (*g*) Meakins, J. C., and Eakin, W. W.: Coronary Thrombosis: Clinical and Pathological Study, Canad. M. A. J. **26**:18, 1932. (*h*) Barnes, A. K., and Ball, R. G.: Incidence and Situation of Myocardial Infarction in One Thousand Consecutive Postmortem Examinations, Am. J. M. Sc. **183**:215, 1932. (*i*) Evans, N.; Ambler, A. C., and Dodson, W.: Coronary Disease: Its Pathogenesis, California & West. Med. **38**:98, 1933. (*j*) Appelbaum, E., and Nicholson, G. H. B.: Occlusive Diseases of the Coronary Arteries: An Analysis of the Pathological Anatomy in One Hundred and Sixty-Eight Cases with Electrocardiographic Cor-

two small series [5c,m] the ratio in the cases reviewed ranged between 5 : 1 and 1.1 : 1. It is obvious from these and our own records that women are definitely less susceptible to coronary occlusion than men, but not to the degree formerly believed.

Age.—The youngest patient in our series was 27 years of age and the oldest 87. The average age at the time of the initial attack was 54 years, and the average age for all patients, regardless of the attack observed, was 55 years. The first attack occurred most commonly in the sixth decade (50 to 59 years), taking place in this period in 33.7 per cent of the cases (table 1 and chart 1). The order of frequency in the other age groups was as follows: 60 to 69 years, 26 per cent; 40 to 49 years, 25 per cent; 30 to 39 years, 10 per cent, and 70 to 79 years, 5.4 per cent.

TABLE 1.—*Sex Distribution in 500 Cases of Occlusion of the Coronary Artery: Clinical Findings in Males and in Females*

	Males	Females
Number	387 (77.4%)	113 (22.6%)
Ratio	3.4:1	
Age: 27-39	33 (8.6%)	6 (5.3%)
40-49	85 (21.9%)	20 (17.9%)
50-59	139 (35.9%)	39 (34.9%)
60-69	103 (26.6%)	38 (34%)
70-87	27 (7%)	10 (8%)
Average Age	54.7 years	56 years
Attack: 1	226 (58.4%)	71 (62.9%)
2	127 (32.8%)	35 (31%)
3	28 (7.2%)	5 (4.4%)
4	4 (1%)	0
?	2 (0.5%)	2 (1.7%)
Mortality	108 (28%)	36 (32%)
Diabetes	26 (6.7%)	30 (26.8%)
Hypertension	219 (56.5%)	90 (80%)
Hypertension + diabetes	228 (59%)	99 (88.3%)
Enlarged heart	215 (58.1%)	84 (74.3%)
Heart failure (2 to 4+)	195 (50.4%)	67 (59.8%)
Pulmonary edema	56 (14.5%)	23 (20.5%)
Shock	205 (52.7%)	58 (51.8%)

Only 10 patients were under 30 years of age. Three were 80 or more at the time of the initial attack. The foregoing age distribution differs from those reported by Conner and Holt [1] and by Bean; [2] in the former's series, although the patients in whom the attack occurred in the sixth decade comprised the largest group, the number of attacks occurring in the fifth decade was greater than that of attacks occurring in the

relation in Thirty-Six of These, Am. Heart J. **10**:662, 1935. (*k*) Saphir, O.; Priest, W. S.; Hamburger, W. W., and Katz, L. N.: Coronary Arteriosclerosis, Coronary Thrombosis and the Resulting Myocardial Changes (Thirty-Four Cases), ibid. **10**:567 and 762, 1935. (*l*) Moritz, A. R., and Beck, C. S.: The Production of a Collateral Circulation to the Heart, ibid. **10**:874, 1935. (*m*) Akerson, I. B.; Dias, J. E., Jr., and Monroe, R. T.: The Incidence of Coronary Artery Sclerosis in the Aged, New England J. Med. **217**:622, 1937. (*n*) Lyon, R. M. M.: Myocardial Infarction: A Pathologic Study, Edinburgh M. J. **45**:285, 1938. Bean.[2]

seventh; in the latter's series the attacks occurred (in order of frequency) in the seventh, sixth and eighth decades.

When the ages at the initial attack in our series are broken into five year periods (chart 2), it is seen that in practically two thirds of

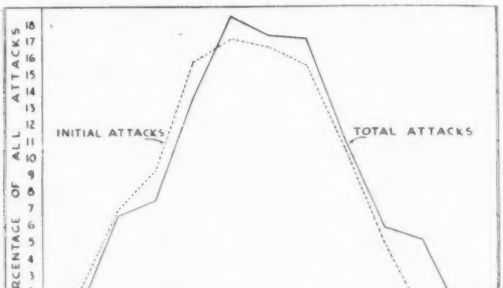

Chart 1.—Age incidence in 500 attacks of coronary occlusion.

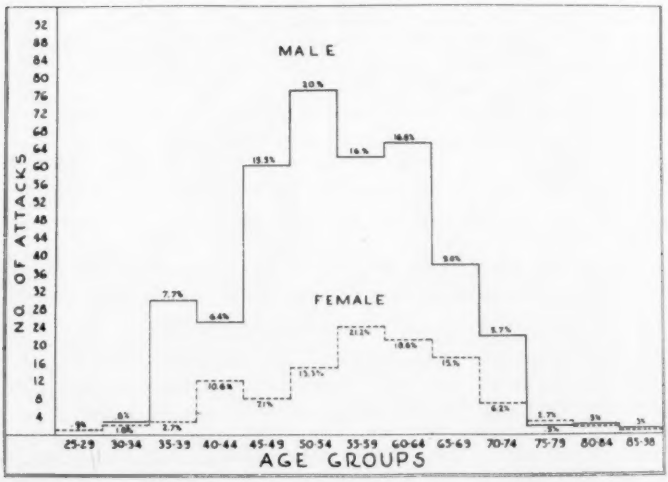

Chart 2.—Age and sex incidence in 500 attacks of coronary occlusion.

the cases the condition occurred between the ages of 45 and 65 years, with an almost equal division among the four five year periods. In most of the series reported in the literature the condition occurred most frequently in patients aged between 50 and 70 years. In our series the

peak was reached in the 50 to 54 year period and not at 60 years as has generally been believed. Actually, there is a sharp rise at 45 years to an incidence only slightly below the peak, so that the incidence between the ages of 45 and 65 varies little. After the age of 65 there is a sharp drop in the number of patients. One third of the attacks in our series occurred before the age of 50 years and one sixth before the age of 45. Similar conclusions can be drawn if all the cases are considered, including those in which there had been previous attacks, except that the number of attacks in the 40 to 49 year period is smaller, i. e., 21 per cent as compared with 24.9 per cent.

When all attacks are considered as against initial attacks alone, there are more patients in the older age groups. The peak still occurs in the sixth decade, which comprises 35.6 per cent of the cases, but the

TABLE 2.—*Age Distribution in 500 Cases of Occlusion of the Coronary Artery: Clinical Findings in Each Age Group*

	Age Group					
	27 to 39	40 to 49	50 to 59	60 to 69	70 to 79	Total
No. of cases	39 (7.8%)	105 (21%)	178 (35.6%)	141 (28.3%)	37 (7.2%)	500
Sex: Male	33 (84.6%)	85 (80.7%)	139 (78.2%)	103 (73%)	27 (73%)	387 (77.4%)
Female	6 (15.2%)	20 (19.3%)	39 (21.8%)	38 (27%)	10 (27%)	113 (22.6%)
Attacks: 1	24 (61.5%)	65 (61.9%)	104 (58.4%)	81 (58%)	23 (62.2%)	297 (59.4%)
2	13 (33.4%)	33 (31.4%)	55 (30.9%)	48 (34%)	10 (27%)	162 (32.3%)
3	2 (5.1%)	6 (5.9%)	15 (8.4%)	6 (4.2%)	4 (10.8%)	33 (6.6%)
4	0	1 (1.1%)	2 (1.1%)	1 (0.7%)	0	4 (0.8%)
?	.....	.....	.....	.....	.....	4 (0.8%)
Mortality rate	6 (15.4%)	22 (20.9%)	43 (24.7%)	60 (42.5%)	13 (36.1%)	144 (28.8%)
Diabetes	2 (5.1%)	5 (3.8%)	19 (10.7%)	20 (14.2%)	10 (27%)	56 (11.2%)
Hypertension	14 (36%)	55 (52.2%)	114 (64%)	104 (74%)	25 (69.5%)	312 (62.4%)
Enlarged heart	14 (35.9%)	51 (48.6%)	106 (59.5%)	98 (69.5%)	29 (78.3%)	299 (59.8%)
Heart failure, 2 to 4+	12 (30.8%)	48 (45.8%)	83 (46.5%)	83 (59%)	25 (69.5%)	252 (50.8%)
Pulmonary edema	5 (12.8%)	18 (17.1%)	35 (19.7%)	23 (16.7%)	8 (22.2%)	79 (15.8%)
Shock	25 (64.1%)	52 (49.5%)	87 (49%)	77 (54.6%)	24 (64.9%)	263 (52.6%)

number of patients in the seventh decade exceeds that in the fifth (28.3 per cent as against 21 per cent [table 2]). The number of patients in the fourth decade is practically the same as that in the eighth, 7.8 per cent and 7.2 per cent.

These results differ in several respects from those reported in the literature. An analysis of 12 clinical series comprising 1,761 cases [6] revealed that the number of attacks in the seventh decade was almost

6. (*a*) Gordinier, H. C.: Coronary Arterial Occlusion, Am. J. M. Sc. **168:** 181, 1924. (*b*) Christian, H. A.: Cardiac Infarction (Coronary Thrombosis): An Easily Diagnosable Condition, Am. Heart J. **1:**129, 1925. (*c*) Coombs, C. F.: Observations on the Etiological Correspondence Between Anginal Pain and Cardiac Infarction, Quart. J. Med. **23:**233, 1930. (*d*) Boas, E. P., and Donner, S.: Coronary Artery Disease in the Working Classes, J. A. M. A. **98:**2186 (June 18) 1932. (*e*) Hochrein, M.: Der Myokardinfarkt: Erkennung, Behandlung und Verhütung, Dresden, Theodore Steinkopff, 1937, p. 4. Conner and Holt.[1] Parkinson and Bedford.[3a] Levine.[3b] Bramwell.[3c] Harrington and Wright.[3d] Willius.[3l] Palmer.[3m]

as great as in the sixth (32 per cent as compared to 35 per cent), while in five series[7] the number of attacks occurring in the seventh decade actually exceeded that observed in the sixth. Also, there was a greater number of patients over 70 than of patients below 40, 10 per cent as against 4 per cent. In summary, our series includes more patients in the younger age groups than have been found in previously published studies.

Of particular interest are the patients in our series under 40 years of age, of whom there were 39, or 7.7 per cent. Of these, 1 was 27 years old, 5 were 30 to 34, and 33 were 35 to 39. If the age at the initial attack alone is considered, it is found that 9.4 per cent of attacks occurred before the patient was 40 years old. The diagnosis in 2 cases in which the initial attack occurred before the age of 30 was confirmed by autopsy. In the literature cited, only 106, or 3.3 per cent, of the patients were below 40. However, in addition, 115 attacks of coronary occlusion occurring before the age of 41 have been collected from case reports, both clinical and based on autopsy.[8] The patients included an

7. Parkinson and Bedford.[3a] Levine.[3b] Christian.[6b] Coombs.[6c] Hochrein.[6e]

8. (*a*) Osler, W.: Disease of the Coronary Arteries, Tr. Path. Soc. Philadelphia **11**:106, 1887-1889. (*b*) Dreschfeld, J.: On Angina Pectoris and Pseudo-Angina, Practitioner **44**:28, 1890. (*c*) Palmer, W. H.: Spontaneous Rupture of the Heart, Boston M. & S. J. **155**:113, 1906. (*d*) Klingman, T.: Spontaneous Rupture of the Heart, New York M. J. **87**:198, 1908. (*e*) Gorham, L. W.: Significance of Transient Localized Pericardial Friction in Coronary Thrombosis, Albany M. Ann. **41**:109, 1920. (*f*) Krumbhaar, E. B., and Crowell, C.: Spontaneous Rupture of the Heart, Am. J. M. Sc. **170**:828, 1925. (*g*) Kerr, W. J.; Larkey, S. L., and Lassan, A. E.: Coronary Occlusion and Myocardial Degeneration, California & West. Med. **23**:46, 1925. (*h*) Nathanson, M. H.: Disease of the Coronary Arteries, Am. J. M. Sc. **170**:240, 1925. (*i*) Jamison, S. C., and Hauser, G. H.: Angina Pectoris in a Youth of Eighteen, J. A. M. A. **85**:1398 (Oct. 31) 1925. (*j*) Clark, G. F.: Coronary Occlusion, U. S. Nav. M. Bull. **23**:487, 1925. (*k*) Benda, C.: Ueber einen Fall von schwerer infantiler Koronararteriensklerose als Todesursache, Virchows Arch. f. path. Anat. **254**:600, 1925. (*l*) Allan, G. A.: Case Presenting Multiple Arterial Thrombosis Including Both Coronaries, Glasgow M. J. **110**:351, 1928. (*m*) Hughes, F. W. T., and Perry, C. B.: Senile Arterial Changes in Child Aged Seven Weeks, Bristol Med.-Chir. J. **46**:219, 1929. (*n*) Herapath, C. E. K., and Perry, C. B.: The Coronary Arteries in a Case of Familial Liability to Sudden Death, Brit. M. J. **1**:685, 1930. (*o*) Werley, G.: Coronary Infarct and Angina with Abdominal Symptoms, M. J. & Rec. **131**:367, 1930. (*p*) Levy, R. L.: Mild Forms of Coronary Thrombosis, Arch. Int. Med. **47**:1 (Jan.) 1931. (*q*) Smith, H. L., and Bartels, E. C.: Coronary Thrombosis with Myocardial Infarction and Hypertrophy in Young Persons: Report of Two Cases with Necropsy, J. A. M. A. **98**: 1072 (March 26) 1932. (*r*) Rathe, H. W.: Sclerosis of the Coronary Arteries with Myocardial Infarction in a Young Woman, Am. Heart J. **9**:539, 1934. (*s*) Leary, T.: Experimental Atherosclerosis in the Rabbit Compared with Human

infant 7 months old, 7 boys and girls aged 10 to 20 years, 8 men and women aged 21 to 30, and 99 patients 31 to 40.

A number of authors have observed that women suffer coronary occlusion at a somewhat later age than men.[9] Conner and Holt [1] found that occlusion is uncommon in women under 50. Of the women observed by them, only 19 per cent were under 50, as compared with 35 per cent of the men. In Howard's [3h] series 54 per cent of the women and only 25 per cent of the men were over 60; there were no women under 40. Hochrein's [6e] patients included 43 men and only 7 women under 50 years but more women than men over 70. Our series shows a similar but less striking difference in this respect. We found that 30.3 per cent of the men and only 23 per cent of the women were under 50. Furthermore, 43.4 per cent of the women were 60 years old or over, as compared with 33.6 per cent of the men. The discrepancy is even greater below the age of 40. In this group there were 33 men and only 6 women, a ratio of 5.5 : 1. This observation has been stressed by other writers.[10] The average age of the men was 53.5 years for the first attack and 54.7 years for all attacks, while that of the women was 55.7 and 56 years respectively. In the series of Levine [3b] and Mullins [3l] also the average age of the women was two years greater than that of the men. The peak incidence among women in our series occurred between the ages of 55 and 59 years, as compared with 50 to 54 years for men.

(Coronary) Atherosclerosis, Arch. Path. **17**:453 (April) 1934. (*t*) Cullinan, E. R., and Graham, G.: Atheroma and Coronary Thrombosis in a Young Diabetic, J. Path. & Bact. **38**:167, 1934. (*u*) White, P. D.: Coronary Disease and Coronary Thrombosis in Youth, J. M. Soc. New Jersey **32**:596, 1935. (*v*) Sprague, H. B., and Orgain, E. S.: Electrocardiographic Study of Cases of Coronary Occlusion Proved at Autopsy at the Massachusetts General Hospital, 1914-1934, New England J. Med. **212**:903, 1935. (*w*) Cooley, L. E.: Longevity After Coronary Thrombosis in a Young Individual, J. Iowa M. Soc. **25**:30, 1935. (*x*) Fernando, P. B.: Coronary Occlusion in a Patient Twenty-Four Years Old, Brit. M. J. **1**:976, 1935. (*y*) May, W. J.: Coronary Infarction in Young Adults, South African M. J. **10**: 772, 1936. (a^1) Glendy, R. E.; Levine, S. A., and White, P. D.: Coronary Disease in Youth: Comparison of One Hundred Patients Under Forty with Three Hundred Persons Past Eighty, J. A. M. A. **109**:1775 (Nov. 27) 1937. (b^1) Burnett, C. T.: Pain and Pain Equivalents in Heart Disease, Ann. Int. Med. **10**: 1156, 1937. (c^1) Stroud, W. D., in discussion on Glendy, Levine and White.[8a1] (d^1) Halbersleben, D.: Coronary Occlusion in a Young Adult, New England J. Med. **218**:175, 1938. (e^1) Durant, T. M.: The Occurrence of Coronary Thrombosis in Young Individuals, Ann. Int. Med. **10**:979, 1937. (f^1) Franklin, M. S.: Coronary Thrombosis in Young Adults, J. Missouri M. A. **35**:32, 1938. (g^1) Scott, E. G.: Coronary Thrombosis in a Twenty-Seven Year Old Man, Virginia M. Monthly **65**:391, 1938.

9. Conner and Holt.[1] Bean.[2] White and Bland.[3e] Lyon.[5n]

10. Glendy, Levine and White.[8a1] Burnett.[8b1] Stroud.[8c1] Halbersleben.[8d1]

Mortality Rate.—We discovered a direct relation between age and mortality rate (table 1 and chart 3). The latter rose from 15.4 per cent in the fourth decade to 42 per cent in the seventh, the average for the entire series being 28.8 per cent. It is to be noted, however, that the mortality rate was practically constant between the ages of 40 and 59 years, ranging between 20 and 24 per cent, while at 60 years there was a sharp rise to 42 per cent, which was maintained until 69 years. At 70 years and above the rate fell to 36 per cent.

A similar trend is observed when the mortality rate for the initial attacks only is considered; the same sharp rise in mortality occurs at the age of 60. The average age was 58 years for the fatal and 53.8 years for the nonfatal attacks. It is interesting to note that in the fourth decade the nonfatal attacks were double the number of fatal attacks,

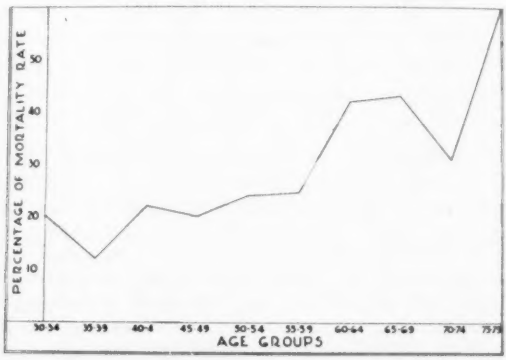

Chart 3.—Mortality rate according to age in 500 attacks of coronary occlusion.

while in the seventh decade the reverse relation was true. A number of authors have remarked similarly on the increasing mortality with age [8i,1] and the favorable prognosis for the young.[11] Willius [8i] and Mullins [8i] did not observe one fatality in a patient below the age of 40. In Levine's [8b] cases of nonfatal occlusion the average age of the patients was 57.8 years, and in his cases of fatal occlusion, 61 years; in Cooksey's [12] series there was an even greater difference, the figures being 54.2 and 63.4 years respectively. In several large clinical series the average age was 55.9 years, as against 57.3 obtained in postmortem studies. In the latter the highest incidence almost invariably occurred in the 61 to 70 year group and not in patients between 51 and 60 years.

11. Bramwell.[8e] Glendy, Levine and White.[8a1] Burnett.[8b1] Stroud.[8c1] Halbersleben.[8d1]

12. Cooksey, W. B.: Coronary Thrombosis: Follow-Up Studies with Especial Reference to Prognosis, J. A. M. A. **104**:2063 (June 8) 1935.

The mortality rate for women in our series was only slightly greater than that for men (32 per cent as against 28 per cent) and the average age of women who died was one year greater than that of men. Willius [3i] and Coombs [6c] found the prognosis poorer for women, but White and Bland [3e] considered the factor of sex unimportant. The increase in mortality has usually been attributed to the greater incidence of diabetes in women.

Multiple Attacks.—The incidence of previous attacks of coronary occlusion was calculated for the patients in each age group. From table 2 it will be seen that the percentage of first, second and third attacks were approximately the same in all decades of life. Fifty-eight to 62 per cent of patients of all ages were treated in their initial attack of occlusion; 31 to 34 per cent of all patients below 70 had suffered at least one previous attack, and 4 to 8.5 per cent, at least two previous attacks. At 70 years and over the incidence of third attacks increased slightly. These figures seem surprising, for one would expect a lower incidence of previous occlusions in the younger age groups. It is apparent, however, that the young patient who has had one attack is as susceptible as the elderly patient to further attacks.

The mortality rate, as was to be expected, increased with each succeeding attack, rising from 23.2 per cent for the initial attack to 35.2 per cent for the second and 39.4 per cent for the third. In each attack, whether the first, second or third, the mortality rate also rose with increasing age.

Diabetes.—The incidence of diabetes mellitus in the entire series studied was 11.2 per cent. In patients not previously known to be diabetic the presence of diabetes was determined by observation of persistent glycosuria and hyperglycemia. It is interesting that this incidence in a series drawn from a predominantly Jewish population was similar to that reported by Conner and Holt,[1] whose patients were mainly non-Jewish.

Diabetes was found by us to be more common in the older patients, occurring in 17 per cent of those aged 60 years and older and in only 4.8 per cent of those under 50. Only 2 patients under 40 and only 7 under 50 were diabetic (table 2). These findings are in accord with those of Warren.[13] In his extensive series of diabetic patients, all those who died of arterial degeneration were over 40 years of age and few were under 50.

Diabetes in our series was also much more common in women than in men, the incidence being 26 per cent in the former and only 6.7 per cent in the latter (table 1). The incidence in women rose directly with age

13. Warren, S.: The Pathology of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1930.

from 4.5 per cent in the fifth decade to approximately 50 per cent in the eighth decade. It rose only slightly in males (chart 4).

The prognosis of the attack in diabetic persons was less favorable than for nondiabetic persons, the mortality rate being 39.3 per cent in the former and 27.5 per cent in the latter. In women the discrepancy was even more marked, the mortality rate for diabetic and for nondiabetic persons being 40 and 22 per cent respectively.

It is clear from these data that diabetes was not a factor in the occurrence of coronary occlusion in men and in young women but that it played a definite role in women over 50 years of age. It is evident from the higher mortality rate that the degree of disease of the coronary arteries in patients with diabetes was greater and the clinical course more severe.

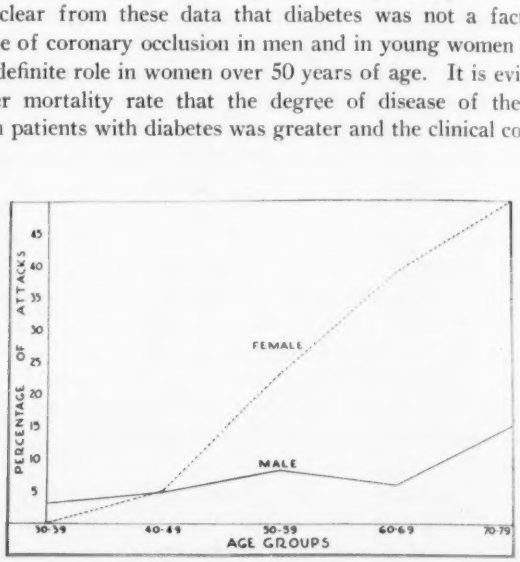

Chart 4.—Diabetes in relation to age and sex.

Hypertension.—Hypertension is a common antecedent of coronary occlusion and was concluded by Levine [8b] to be the most significant single etiologic factor, since it occurred in at least 40 per cent of his patients. Other authors have reported the incidence to be from 33 to 73 per cent.[14] Allen [14] compared the incidence of hypertension in patients who had had coronary occlusion and in the general population and found it definitely higher in the former. In our series hypertension (as evidenced by a systolic pressure of 150 mm. or more or a diastolic pressure of 90 mm. or more) was present in 62.4 per cent of cases (table 2). It should be noted that many authors have considered hypertension to be present only when the systolic pressure was 160 mm. or the diastolic pressure 100 mm.; they have, therefore, obtained lower percentages than

14. Allen, W.: The Relation of Arterial Hypertension to Angina Pectoris and Coronary Occlusion, South. Med. & Surg. **96**:377, 1934.

ours. However, since most patients with coronary occlusion are seen after the blood pressure has fallen, we believe that the figure of 62.4 per cent is lower than the actual incidence.

The frequency of hypertension rose directly with increasing age. From chart 5 it is seen that the incidence rose in a practically straight line from 28 per cent in men 25 to 34 years of age to 80 per cent in those aged 75 years and older. In females the incidence rose more rapidly from a similar figure of 25 per cent in those below 35 years to 90 to 100 per cent in those aged 45 years and older.

There was a definite difference between the sexes in the incidence of hypertension. Eighty per cent of the women in our series had hypertension, as compared with only 56.5 per cent of the men. Furthermore, hypertension or diabetes was present in 88.3 per cent of women and

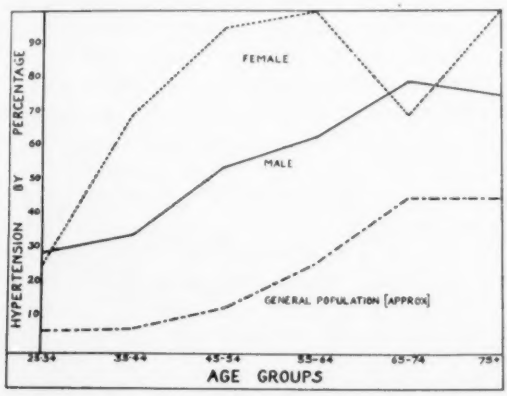

Chart 5.—Hypertension in the various age groups in 500 cases of coronary occlusion as compared to hypertension in the general population.

in only 59 per cent of men. It is thus seen that preceding hypertension or diabetes or both are present in the vast majority of women with coronary occlusion.

Hypertension did not affect the immediate prognosis, for the mortality rate was approximately the same for both hypertensive and nonhypertensive patients, in spite of a considerable increase in the incidence of heart failure and cardiac enlargement in the former. Conner and Holt [1] and Vander Veer and Brown [31] also found no relation between hypertension and the mortality rate.

Cardiac Enlargement.—Closely related to the frequency of hypertension was that of cardiac enlargement, which was present in 59.8 per cent of cases. There was a direct correlation with age, for the incidence was only 35.9 per cent in patients below 40 but it rose

rapidly to a peak of 78.3 per cent in patients over 70 (table 2). Cardiac enlargement was more common in women than in men, occurring in 74 per cent of the former but in only 58 per cent of the latter, presumably because of the greater frequency of hypertension in women. Furthermore, women comprised 28 per cent of patients with enlarged hearts but only 14 per cent of those with normal-sized hearts.

The importance of cardiac enlargement lies in its close association with heart failure, which is the principal cause of death in cases of coronary occlusion and occurs almost always in the presence of an enlarged heart.[15] Conversely, the favorable prognosis which we have found for young persons may well depend on the low incidence of cardiac enlargement in persons below 40 or 45 years of age. White and Bland [3e] and Allen [3f] also found a correlation between cardiac enlargement and the mortality rate.

Heart Failure.—Congestive heart failure was closely associated with cardiac enlargement, occurring in moderate or severe degree in 50.8 per cent of our patients. When slight degrees of failure were included, the incidence was 69 per cent, rising progressively with increasing age from 30.8 in the fourth decade to 69.5 per cent in the eighth, and was slightly higher in women than in men. As has been stated, it can probably be accounted for by the greater frequency of cardiac enlargement in women and in older patients.

An interesting finding was that pulmonary edema was more common in women than in men, the incidence being 20.5 and 14.5 per cent respectively. It is in these patients, particularly in women, that pain may be minimal during the attack, being masked by the pulmonary edema.

Shock.—Symptoms of shock occurred in approximately one-half the patients and were equally common in men and women. The incidence was slightly greater in patients below 40 and in those aged 70 years or over, but this difference may not be significant, because the number of patients in these groups was relatively small. In view of the low mortality rate for young patients, the high incidence of shock in them suggests that shock alone is not of serious import as far as recovery is concerned but that heart failure, which is more common in older patients, is the dominant factor in the immediate prognosis.

Mode of Death.—In a previous study [15] it was shown that the most common cause of death in cases of coronary occlusion is congestive heart failure. It was the chief cause of death in 33 per cent of cases analyzed by us and in 16.5 per cent of additional cases it was associated

15. Master, A. M.; Dack, S., and Jaffe, H. L.: Coronary Thrombosis: An Investigation of Heart Failure and Other Factors in Its Course and Prognosis. Am. Heart J. **13**:330, 1937.

with severe shock. Death in one-half the cases, therefore, was due to heart failure with or without shock. In patients below 50 years of age, however, death from heart failure occurred in only 30.7 per cent of cases. This is to be expected (we have already drawn attention to the lower incidence of heart failure in the young). In patients under 50 the most common cause of death was arterial embolism, either peripheral or pulmonary. The incidence of this complication as the cause of death in such patients was 53 per cent, as compared with only 12 per cent in patients aged 50 years or more. Sudden death, too, was somewhat less common below 50. There were no differences in the cause of death between men and women.

COMMENT

Our findings, like those of other authors, indicate that persons of middle age and not of old age comprise the great majority of those suffering from acute coronary occlusion. In our series the condition was most common in patients aged 50 to 59 years, and it occurred almost as often in patients under 50 years as in those over 60. When the age at the initial attack was considered it was found that the peak was approached at the early age of 45 years. These figures, however, do not indicate the true incidence of coronary occlusion in each age group, for this depends on the age distribution of the general population as well. The finding of fewer patients in our series between the ages of 60 to 64 years than between 50 and 54 years, therefore, may be due to the fact that there are fewer persons in the former age group in the general population, since there is a progressive decrease in population above the age of 45 years.[16] Therefore, in order to evaluate more accurately the influence of increasing age on the incidence of coronary occlusion, the number of cases in each ten year age group was correlated with the age distribution in the general population. This correlation was made for all patients as well as for men and women separately (chart 6). A figure was obtained for each age group which expressed the number of attacks of coronary occlusion per unit of general population in that age group. This figure is of value only when compared with the ratios for each age group. Since our series was collected in a hospital the patients of which are predominantly Jewish, we have taken as our basis the estimated Jewish population in New York city.[17] In this group there is a progressive decrease in population above the age of 44.

16. Federal Census for New York City, April 1, 1930.

17. Studies in the New York Jewish Population, New York, Bureau of Jewish Social Research, 1928, pp. 14-18.

It is seen in chart 6 that the number of attacks per unit of population rose progressively in each age group until the age of 74 years. Above this age there was an abrupt fall in the incidence of attacks; this has not been shown on the graph because of the small number of cases in our series in this age group. It is interesting, however, that in a recent survey [18] of deaths from disease of the coronary arteries among insured persons there was a similar falling off after the age of 70 years. When the two sexes were compared it was found that the ratio of attacks in men per unit of male population rose more abruptly with age than did the ratio of attacks in women per unit of female population, particularly in the younger age groups. This again emphasizes the greater incidence of coronary occlusion in males than in females.

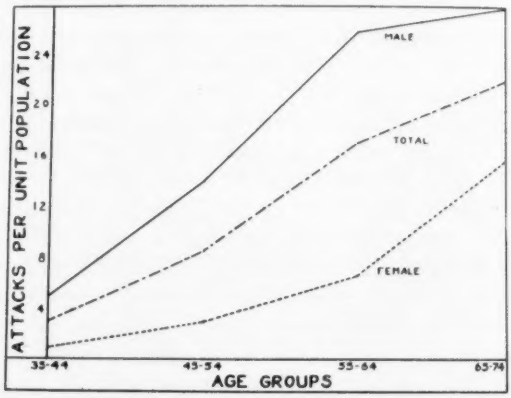

Chart 6.—Ratio of attacks of coronary occlusion to the estimated Jewish population of New York city.

While these observations suggest that the occurrence of coronary occlusion is associated with increase in age, a study of the influence of hypertension and a correlation of hypertension with age indicate that such a conclusion is not entirely warranted. We have pointed out (chart 5) that hypertension was present in only 28 per cent of men in our series below 35 years of age but that the incidence rose rapidly with age, reaching 80 per cent at the age of 70. In women hypertension was even more common, being present in 90 per cent of those over 44 years of age. Hypertension would seem, therefore, to be an important predisposing factor in coronary occlusion, particularly in the older age groups and in women. Before this conclusion is accepted, however, the incidence of hypertension in our series should be com-

18. Muhlberg, W., Medical Director, Union Central Insurance Company, Cincinnati, Ohio: Personal communication to the authors.

pared with that in the general population. Accurate figures for the latter, unfortunately, are practically impossible to obtain at present. Although there are a few reports [19] comprising the cases of 42,000 persons, they give only an approximate incidence of hypertension in the various age groups. In addition, the number of persons in each group is relatively small. These studies show that the incidence of hypertension is approximately 5 per cent at the age of 25 and rises progressively to 26 per cent at the age of 55 and to 45 per cent above the age of 65 (chart 5). It is obvious that the incidence of hypertension in the 25 to 54 year group of males and females was about four or five times as high in our series as in the general population; in the 55 to 74 year group it was two or three times as high. This confirms the importance of hypertension as a precursor of coronary occlusion, particularly in young persons.

Of even greater significance in this connection are the conclusions regarding hypertension to be drawn from chart 7. It has been prepared in a similar manner to chart 6; that is, the male population in each age group has been broken down into hypertensive and nonhypertensive persons by applying the approximate percentages of hypertension derived for the general population. In each age group we calculated both the ratio of hypertensive men in our series to those in the general population and the ratio for those with normal blood pressure. Since the calculated percentages of hypertensive males in the general popula-

19. Thompson, R. J. C., and Todd, F. R. E.: Old Age and Blood Pressure Problems, J. Roy. Army M. Corps **40**:192, 1923. Alverez, W. C.; Wulzen, R., and Mahoney, L. J.: Blood Pressures in Fifteen Thousand University Freshmen, Arch. Int. Med. **32**:17 (July) 1923. Weitz, W.: Zur Aetologie der genuinen oder vascularen Hypertension, Ztschr. f. klin. Med. **96**:151, 1923. Dunham, G. C.: Variation in Blood Pressure as Associated with Variation in Age and Body Weight, Internat. Clin. **3**:81, 1925. Diehl, H. S., and Sutherland, K. H.: Systolic Blood Pressures in Young Men, Including a Special Study of Those with Hypertension, Arch. Int. Med. **36**:151 (Aug.) 1925. Life Conservation Studies: I. Physical Impairment Among Office Workers; II. Physical Impairment Among Industrial Workers, Cincinnati, The Heart Council of Greater Cincinnati, 1925. Richter, A.: Ueber Blutdruck im höheren Lebensalter, zugleich ein Beitrag zur Klinik des Hochdrucks, Deutsches Arch. f. klin. Med. **148**:111, 1925. Britten, R. H., and Thompson, L. R.: Occupations: A Health Study of Ten Thousand Male Industrial Workers, Public Health Bulletin 162, United States Public Health Service, June 1926. Gelman, J.: Hypertoniestudien: Alters- und Berufsverschiebungen im hämodynamischen System, Ztschr. f. klin. Med. **106**:310, 1927. Saller, K.: Ueber die Altersveränderungen des Blutdrucks, Ztschr. f. d. ges. exper. Med. **58**:683, 1928. Riseman, J. E. F., and Weiss, S.: The Age and Sex Incidence of Arterial Hypertension, Am. Heart J. **5**:172, 1929. Musser, J. H., and Phillips, A. W.: Comparison of Blood Pressure, Blood Urea Nitrogen, Phenolsulphonephthalein, and Urine Tests in the Aged, J. Lab. & Clin. Med. **15**:633, 1930. Davis, H. J.: Notes on Blood Pressure in Old Age, Human Biol. **2**: 264, 1930. Willius, F. A.: Heart and Old Age: Study of Seven Hundred Patients Seventy-Five Years and Older, Am. J. M. Sc. **182**:1, 1931.

tion are only approximations, we applied a ±10 per cent correction to each ratio obtained and plotted them as a band instead of a single line. The ratios for the age groups from 25 to 34 and from 75 to 84 were omitted because of the small number of cases.

It is seen that the ratio of hypertensive attacks to the hypertensive male population rises steeply with increasing age until 64 years and then falls slightly. The ratio doubles between the ages of 35 and 55. Although the incidence of coronary occlusion per unit of population is not so great in the nonhypertensive group, it, too, rises with age in about the same proportion as in the hypertensive group. Between the ages of 35 and 74 years coronary occlusion is from five to eight times as frequent in hypertensive as in nonhypertensive persons, but the

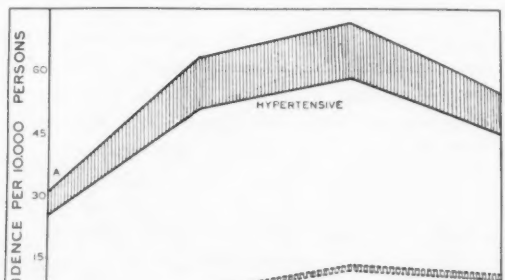

Chart 7.—Ratio of attacks of coronary occlusion to the estimated Jewish population of New York city in relation to hypertension.

incidence in both groups rises with age in about the same degree. Hypertension, therefore, plays the paramount role in the increasing incidence of coronary occlusion, but age alone also plays a part. Arteriosclerosis is the fundamental pathologic basis, but hypertension accelerates this process tremendously, particularly in the younger age groups.

These findings emphasize the importance of hypertension in coronary occlusion, but its exact role cannot be evaluated until more accurate figures on the incidence of hypertension in the general population are obtained. The arteriosclerotic process in the coronary arteries occurs spontaneously in some persons at a relatively early age but in the majority is preceded by hypertension.

That hypertension is not the only factor in coronary occlusion is evident. The majority of our patients under 45 were nonhypertensive. The blood pressure was also normal in cases of young persons cited by Durant [8e1] and Franklin.[8f1] Other predisposing factors have therefore been sought. Some authors have claimed that syphilis is common as

a cause of coronary occlusion in the young. This conclusion was not borne out in our series, for there were only 2 patients below 50 in whose cases the Wassermann reaction was positive; since both are living at the time of this report, it is uncertain whether the closure was a result of syphilitic stenosis of a coronary ostium or of arteriosclerosis of the coronary arteries. Occlusion of a coronary artery has also been attributed to rheumatic fever; but rheumatic heart disease was present in only 1 of our young patients, and this was coincidental. It is also noteworthy that diabetes was uncommon in our young patients, whether male or female. Warren found that diabetic patients usually had coronary occlusion after the age of 50. We are tempted, therefore, as several authors before us have done,[20] to invoke a familial tendency as an explanation of the occurrence of coronary sclerosis and occlusion in young persons. In our series, however, the incidence of heart disease in the immediate families of the young patients was found to be no greater than that in the families of the older ones.

The influence of hypertension on prognosis is not entirely clear. We have seen that for the young, with little hypertension, the prognosis was good and that for women, with more hypertension, the mortality rate was slightly higher than in men. However, the prognosis in the entire series was similar for the patients with and for those without hypertension, in spite of the higher incidence of cardiac enlargement and heart failure in men and women with hypertension. Conner and Holt,[1] too, found hypertension of no significance in the prognosis of an attack. It is evident that, while hypertension may predispose to coronary sclerosis and occlusion, the hypertensive patient progresses as well as the nonhypertensive patient after the occlusion has occurred. It is even possible that the increased blood pressure has a favorable influence on the coronary blood flow after occlusion.

Some investigators have held that the frequency of coronary occlusion at present is greater than formerly, particularly in the younger age groups. It seems more likely, however, that the increase is only apparent and is the result of greater accuracy in diagnosis and of greater interest in the disease. Knowledge of the frequency of coronary occlusion in young as well as in old persons is becoming widespread. Not only physicians but lay persons are more apt now to recognize mild or atypical attacks. Such a diagnosis as acute indigestion is no longer accepted without question. Furthermore, the increasing use of the electrocardiograph brings to light instances in which the condition has been unsuspected or diagnosed as angina pectoris.

Nor is it necessary to postulate that disease of the coronary arteries and therefore occlusion appears at an earlier age today than formerly.

20. Musser, J. H., and Barton, J. C.: The Familial Tendency of Coronary Disease, Am. Heart J. **7**:45, 1931. Levine,[3b] Herapath and Perry,[8n] Glendy, Levine and White.[8a1]

In a previous paper [21] we have shown that in the young the coronary vessels may be involved long before other arteries become sclerotic. In 9 cases in which arteriosclerosis was present only in the coronary arteries 8 of the patients were under 45 years of age. It would seem, therefore, that certain persons are susceptible to coronary sclerosis and occlusion and that this process often begins at a relatively early age and may remain localized to the coronary arteries. In the majority of young patients the retinal arteries were normal. In this connection our data concerning multiple attacks are pertinent. It was found that the incidence of first, second and third attacks was similar in each age group; that is, after an initial attack of coronary occlusion a man or woman 45 or 50 years old was as apt to have another attack as a person of 60 or 65. Apparently, once the sclerotic process is initiated its tempo is the same at all ages.

It is interesting to compare the course of coronary occlusion in the young and in the old. The outstanding difference is the much better prognosis for the former; even in the first attack the mortality rate rises with age. This relation, however, is not a direct one in all decades. It has been pointed out that the mortality rate rose gradually during the period from 45 to 59 years and then increased sharply, beginning at the age of 60. It is probable that after the fifties the degree of coronary sclerosis and myocardial involvement becomes definitely more advanced, so that a difference of even a few years about the age of 60 may be significant in prognosis. At first it may seem surprising that the prognosis is better for the young than for the old, for anastomoses are thought to manifest themselves only as a result of increasing disease of the coronary arteries and so appear in later years. It is apparent, therefore, that the outcome of the attack depends on other factors in addition to vascular anastomoses. Postmortem studies have indicated [22] that in the young the coronary disease may not be widespread but often may be localized to only one or two arteries; consequently, the heart muscle as a whole is in good condition and can withstand the occlusion of the diseased artery. Indeed, we have seen that for young persons the incidence of cardiac enlargement and heart failure is much lower than for the old, pointing to the reserve strength of the heart and accounting for the rarity of a fatal issue. Actually, death in the young is more often the result of a complication of the occlusion (particularly embolism) than of cardiac failure. Another point in favor of the survival of young persons is the lesser degree or total absence of arteriosclerosis outside the heart. The kidneys, brain and other organs often remain unaffected.

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21. Master, A. M.; Dack, S., and Jaffe, H. L.: Coronary Artery Thrombosis: Mode of Death and Analysis of Fatal Cases, New York State J. Med. **37**:1707, 1937.

22. Leary.[88] Master, Dack and Jaffe.[15]

We have shown that the sexes exhibit several interesting differences in respect to coronary occlusion, including incidence, age, frequency of hypertension, frequency of diabetes and mortality rate. Formerly it was believed that coronary occlusion was rare in women, the ratio of men to women being given as 10:1 to 5:1. Recently it has been pointed out that women are more frequently affected, in the proportion of 5:1 to 3:1. In our series the ratio was 3.4 to 1. The explanation of this change doubtless lies in the improved methods of diagnosis of and search for coronary occlusion, as we have discussed in a previous paragraph in the case of young persons. Unless one is on the alert for the presence of coronary occlusion in women one may miss the diagnosis entirely. It is probable that in the past coronary occlusion in women not infrequently has been labeled acute cholecystitis. In addition, it is our impression, based on insufficient data, that women are less apt than men to have severe, persistent pain and that the attack is more likely to begin with pulmonary edema, which may mask the pain. In such cases the diagnosis may be difficult to make. It may be mentioned that few women in our series smoked, and none immoderately. Tobacco, therefore, is not the cause of the apparent increase in coronary occlusion in women.

Many authors have found that coronary occlusion occurs at a later age in women than in men. Our experience confirms this observation. The greater susceptibility of older women to coronary occlusion may account for the rapid increase in the incidence of diabetes in women over 50; diabetes did not become more frequent with age in the males.

Another difference between the sexes was the higher incidence of hypertension in women. Only 1 of every 10 women with coronary occlusion failed to show either hypertension or diabetes; the ratio for women of 60 years and over was only 1 in 12. It is difficult to explain this difference; coronary sclerosis often occurs in men without diabetes or hypertension, but the foundation for this disease in women is laid by one of these factors. It is probable that when coronary occlusion occurs in women the sclerosis is more widespread and severe than in men, and as a result of hypertension the incidence of cardiac enlargement and heart failure is greater. This probably accounts for the higher mortality in women than in men (32 per cent as against 28 per cent). We have shown [15] that the mortality rate is directly dependent on cardiac enlargement and heart failure.

SUMMARY

The influence of age, sex and hypertension on the incidence, clinical course and prognosis of coronary occlusion has been analyzed in 500 consecutive cases.

Approximately two thirds of the attacks occurred between the ages of 45 and 65, and almost one third before 50 years. The peak occurred in the sixth decade.

The number of initial attacks rose progressively until the age of 45; then a level was maintained until the age of 64, after which there was a rapid decrease. However, when the number of attacks was correlated with the census of the general population in each age group, there was a progressive rise in the incidence of attacks with advancing age to 74 years.

Particular attention was paid to a group of 39 patients aged 27 to 39 years. The susceptibility of these young persons to coronary sclerosis and occlusion could not be attributed to rheumatic fever, syphilis, diabetes, hypertension or a familial or hereditary trait.

The mortality rate varied with age, increasing gradually until the age of 59 and rising sharply in the older age groups. Coronary occlusion is rarely fatal below the age of 40, since the occlusive process is often localized to one artery and the myocardium is not diffusely damaged.

The frequency of multiple attacks was the same in all age groups. Young and old persons are equally susceptible to subsequent attacks of coronary occlusion after an initial attack.

The commonest cause of death before the age of 50 was arterial embolism; after 50, it was cardiac failure.

The ratio of men to women was only 3.4 : 1. The average age of the women was higher than that of the men, and the incidence in women below the age of 40 was relatively small.

Diabetes was frequent in women over 50 but uncommon in men below 70. In women the incidence rose sharply with increasing age.

Cardiac enlargement and heart failure increased with age, being uncommon in the young. They were more common in women than in men. Pulmonary edema with little or no pain not infrequently initiated an attack, particularly in women.

Hypertension occurred in more than half the men and in four fifths of the women. The incidence rose with age from 36 per cent in the fourth decade to 74 per cent in the seventh decade. There was no effect on the mortality rate.

Hypertension is an etiologic factor in coronary occlusion, for its incidence in our series was definitely greater than that calculated for the general population. Furthermore, the ratio of attacks per unit of the hypertensive male population was five to eight times as great as that for patients with normal blood pressure, although both ratios increased with age in the same proportion. Hypertension accelerates the aging process.

Mr. Herbert Marks, assistant statistician of the Metropolitan Life Insurance Company, New York, assisted in the compilation of the data presented in this paper.

JUVENILE DIABETES MELLITUS

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The purpose of this report is to review certain statistical findings on juvenile diabetes mellitus for comparison with other reports and to emphasize some of the features that become apparent from the study. The children studied have not all been continuously under our personal observation from the onset of diabetes, many having had previous treatment elsewhere and others having moved to other locations and supervision. In most cases, however, we have been able to follow their progress.

There were 341 children in this group, all the children with diabetes observed by us between April 1920 and January 1938 except 2 seen in 1917. In all of them diabetes developed before the sixteenth birthday, the earliest onset being at the age of 8 weeks and only 4 children being under 1 year of age when the disease was discovered. The children have been cared for in private practice, at the Children's Hospital since 1922, at the Cedars of Lebanon Hospital since 1930 and at the Los Angeles General Hospital since 1932.

The sex incidence in this series conforms on the whole to that noted by others, the patients being almost equally divided, with a slight preponderance of girls (184) over boys (157). Thirty-seven children (10.8 per cent) of the entire group were Jewish, and of the non-Jewish children 7 were Mexicans, 6 Negroes, 1 Italian, 1 Assyrian and 1 Portuguese. The sex distribution by age at onset is given in table 1.

The incidence of diabetes according to age at onset in this group does not correspond accurately with other reports. The highest peak for the entire group occurred at the 11 to 12 year period (chart 1), but there was another high peak at the age of 7 to 8 years. The peaks for girls occurred at 3 to 4 and 7 to 8 years, with a constant high level at 9 to 10, 10 to 11 and 11 to 12 years, while for boys 7 to 8 and 11 to 12 were the outstanding ages. The sharp drop in incidence of onset during the fifteenth year seems to be universally observed.

HEREDITY

A positive family history of diabetes was obtained in 110 cases. In 216 there was no known diabetes, and in 15 it was unknown whether diabetes had existed in the antecedents. This represents a known incidence of 32.2 per cent. Of the Jewish group (37 children) the data are known for 36, 17 (46 per cent) of whom had a family history of diabetes. In the non-Jewish group the data are known in 304 instances, in 93 (30.6 per cent) of which there was a definite family history of diabetes. Of the children who had had diabetes for ten years or longer (in 4 instances the family history was unknown), 36.9 per cent were known to have a family history of diabetes.

There was a pair of twins who had diabetes. They were Jewish girls. In 1 of them diabetes developed at the age of 3 years 2 months, and in the other, at 3 years 11 months. They are both living at the time of writing, the duration of the disease being six years seven months and five years ten months respectively. Each of the 2 boys had a twin

TABLE 1.—*Distribution by Age at Onset*

Age at Onset, Yr.	Patients	Boys	Girls	Non-Jewish	Jewish
0-5	92	43	49	86	6
6-10	126	54	72	110	16
11-15	123	60	63	108	15
Totals	341	157	184	304	37

brother, and 1 girl had a twin sister. These nondiabetic twins are kept under constant observation, but at the time of writing none have shown any signs of diabetes. The twins with diabetes had a family history of the condition, and one of the other twins also had such a history.

PREVIOUS ILLNESSES

Illnesses prior to the onset of diabetes have been stressed as of etiologic importance. While acute illnesses, especially infections, do lower carbohydrate tolerance and make existing diabetes more severe, for only 24 per cent of this entire group did we obtain a history of an acute illness sufficiently close to the onset of recognizable symptoms to be considered a possible causative factor or precipitating event. On the whole, the records of preceding illnesses varied little from those obtained in the cases of other children of similar age.

Table 2 lists the conditions observed. The patients are classified according to age at onset to bring out the difference in frequency of certain conditions and infections at different ages. The table also indicates conditions occurring within one year of the onset of symptoms and conditions which seemingly precipitated the symptoms of diabetes.

Eighty-two patients (24 per cent) had conditions which were seemingly precipitating, and of these, infections were the factors in 58, or 70.7 per cent. Severe infections of the respiratory tract acting as precipitating factors accounted for 60 per cent of the 58 infections.

Tonsillectomy precipitated symptoms in 5 instances. Serum and vaccine reactions seemed to be the precipitating factors in 7 others, but we were probably told only of the reactions that were followed by symptoms, no mention being made of the many in which symptoms did not follow.

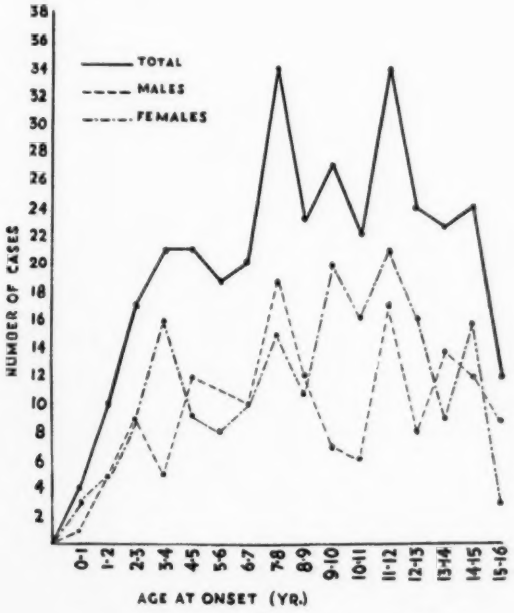

Chart 1.—Incidence according to age at onset.

SYMPTOMS AND DIAGNOSIS

The symptoms of diabetes in this group tended to follow the classic pattern. From 329 records in which the original symptoms were adequately described we found that polyuria occurred in 91.4 per cent of the cases, polydipsia in 89 per cent, loss of weight and strength in 79 per cent and polyphagia in 73.2 per cent. Table 3 shows these data and also indicates that there is little difference when the patients are divided as to age of onset.

TABLE 2.—*Illnesses Before Onset of Diabetes*

History of	Age 0-5 Yr.			Age 6-10 Yr.			Age 11-15 Yr.		
	Total	Within 1 Yr.	Precipitating Symptoms of Diabetes	Total	Within 1 Yr.	Precipitating Symptoms of Diabetes	Total	Within 1 Yr.	Precipitating Symptoms of Diabetes
Measles	14	3	0	77	4	2	86	0	1
Mumps	3	0	0	25	2	0	34	0	1
Chickenpox	12	1	0	49	2	0	53	0	0
Infection of respiratory tract (severe)	41	0	10	48	0	16	41	0	8
Pertussis	21	3	1	62	0	1	51	0	0
Pneumonia	2	0	2	11	2	0	9	0	1
Smallpox	0	0	0	2	0	0	4	0	0
Scarlet fever	1	1	0	10	3	0	15	0	1
Diphtheria	0	0	0	4	1	0	4	0	0
Tonsilitis	15	2	3	25	2	3	19	0	1
Tonsilectomy	9	2	1	28	1	2	47	1	2
Obesity	6	0	0	5	0	0	11	0	0
Constipation	21	0	0	13	0	0	16	0	0
Appendicitis	1	1	0	3	1	0	1	0	0
Appendectomy	1	1	0	1	0	0	0	0	0
Allergy	5	0	0	6	0	0	4	0	0
Malnutrition	1	0	0	0	0	0	1	0	0
Rickets	1	0	0	1	0	0	0	0	0
Automobile accident	3	0	0	2	1	1	1	0	0
Abdominal pain and convulsions	1	0	0	0	0	0	0	0	0
Jaundice	1	0	0	0	0	0	1	0	0
Enteritis and colitis, acute	1	1	0	3	1	0	3	0	0
Torticollis	1	0	0	1	0	0	0	0	0
Papular rash (?)	1	0	1	0	0	0	0	0	0
Styes	1	0	0	0	0	0	1	0	0
Fracture of arm	3	0	0	3	0	0	2	0	0
Fracture of leg	1	0	0	0	0	0	1	0	0
Fracture of clavicle	1	0	0	0	0	0	0	0	0
Severe burn	1	0	0	0	0	0	1	0	0
Ichthyosis	1	0	0	1	0	0	0	0	0
Harelip and cleft palate	1	0	0	0	0	0	0	0	0
Acidosis and vomiting	2	0	0	3	0	0	0	0	0
Swallowed acid	1	0	0	0	0	0	0	0	0
Birthmark removed by cautery	1	0	0	0	0	0	0	0	0
Diarrhea	3	0	2	1	0	0	0	0	0
Hernia, inguinal	1	0	0	0	0	0	0	0	0
Hernia, umbilical	1	0	0	0	0	0	0	0	0
Fever (undetermined origin)	1	0	1	1	1	0	1	1	0
Sarcoid of Beck	1	0	1	0	0	0	0	0	0
Constipation with fever	1	0	1	0	0	0	0	0	0
Herniotomy				3	0	0	0	0	0
Mastoiditis (in 1 case associated with sinus thrombosis)				2	0	1	1	0	0
Mastoidectomy				2	0	1	1	0	0
Cretinism				1	0	0	0	0	0
Furunculosis				4	0	0	2	1	0
Cellulitis: Face				1	0	1	0	0	0
Wrist				..	..	..	1	0	1
Foot				..	..	..	1	0	0
Reaction to pertussis vaccine				1	0	1	0	0	0
Reaction to diphtheria antitoxin				1	0	1	0	0	0
Reaction to smallpox vaccination				2	0	2	1	0	1
Reaction to tetanus antitoxin				1	0	1	0	0	0
Serum sickness				1	0	1	0	0	0
Pyelitis				2	0	0	1	0	0
Damaged heart after diphtheria				1	0	0	0	0	0
Concussion				1	1	0	0	0	0
Undescended testis				1	0	0	0	0	0
Adenitis				1	0	0	3	0	0
Enlarged abdomen				1	0	1	0	0	0
Enlarged thymus				1	0	0	0	0	0
Eczema				1	0	0	0	0	0
Exophthalmic goiter				1	0	0	0	0	0
Thyroidectomy				1	0	1	0	0	0
Pinworms				1	0	0	0	0	0
Chorea				1	0	0	0	0	0
Tuberculosis of spine				1	0	0	0	0	0
Tuberculosis, pulmonary				1	0	0	3	0	0
Traumatic ulcer							2	0	1
Dengue fever							1	1	0
Injury to back							3	0	2
Injury to head							4	0	1
Bursitis							1	0	0
Renal colic with hematuria							1	0	0
Infection from vaccination							1	0	0
Operation for congenital hip disease							1	0	0
Quinsy with operation							1	0	0
Rheumatic fever							1	0	0
Gonorrheal vaginitis							1	0	0
Epilepsy							1	0	0
Abscess of ear							1	0	1
Heel torn off							1	0	0
Typhoid fever							1	0	0

We have analyzed the type of onset of symptoms only from the standpoint of whether it was acute or gradual. The onset was classified as acute if the symptoms developed to the point of being brought to attention on a given day or within about two weeks. If symptoms were noted later the onset was classified as gradual. The aforementioned 329 records are classified in table 4 as to age of onset.

Two hundred and sixty-five records included sufficient data to permit calculation of the number of days elapsing between the onset of symp-

TABLE 3.—*Age at Onset of Symptoms*

Symptom	Entire Group	Onset 0-5 Yr.	Onset 6-10 Yr.	Onset 11-15 Yr.
Polyuria	91.4%	90.9%	93.3%	90.0%
Polydipsia	89.0%	88.6%	90.9%	87.5%
Loss of weight	79.0%	75.0%	81.0%	80.8%
Polyphagia	73.2%	69.3%	75.2%	74.1%

TABLE 4.—*Type of Onset*

Age at Onset, Years	Total Patients	Acute Onset	Gradual Onset
0-5	89	88.5%	11.5%
6-10	122	82.8%	17.2%
11-15	118	78.8%	21.2%

TABLE 5.—*Age at Onset Correlated with Time Elapsing Before Sugar Was Found*

Age of Onset, Years	Average Number of Days Before Sugar Was Found
0-5	38
6-10	49.9
11-15	74.1

toms and the discovery of sugar. In spite of the typical nature of the symptoms and the acuteness of the onset, diagnosis was delayed for an average of fifty-four and five-tenths days for the entire group. The younger children group fared better than the older ones (table 5), obviously because the bathroom habits and general condition of the younger children were watched more closely. This was probably also true for the medical observation.

The unhappy significance of this delay in diagnosis is illustrated by the fact that among 274 patients on whom we had definite data as to the existence of acidosis when the diagnosis of diabetes was made,

approximately 4 of every 10 (37.2 per cent) had more or less severe ketosis, and 1 of every 5 (21.1 per cent) was in coma. Table 6 gives the distribution of ketosis and coma by age groups. Consideration of the data leaves much to be desired in the promptness with which the diagnosis is made and treatment instituted, particularly in the younger group, in which only 31.5 per cent demonstrated no acidosis at the time the diagnosis was made.

MORTALITY

The present status of 315 of these children is known. Fifty-five of them died (table 7). The remaining 26 were lost sight of. The total known mortality of the group was 16.1 per cent with a possible mortality of 23.7 per cent if all those unaccounted for are dead.

Insulin was first available to our patients in November 1922. Prior to this, diabetes had developed in 25, 16 of whom are known to be dead. Fourteen of the deaths occurred before the advent of insulin. Of this group not receiving insulin, 8 died within one month of the onset of

TABLE 6.—*Age Incidence of Ketosis and Coma*

Age at Onset, Years	Total No. of Patients	Ketosis, Percentage	Coma, Percentage	No Acidosis, Percentage
0-5	76	47.4	21.1	31.5
6-10	99	35.4	18 2	46.4
11-15	99	32.4	25.2	42.4

symptoms, 1 lived for seven years, 1 for six years, and 4 from two years and one month to two years and eight months. One hundred per cent, then, of those who did not receive insulin died, and 57 per cent of these died within the first month. The shortest duration of diabetes was five days, and the average was one year and seven months. Eleven, then, lived long enough to receive insulin. Of these, 8 are living, 1 is unaccounted for but was living when last heard from (one year previous to this study) and 2 are dead, each having lived five years and seven months after the onset of symptoms. Chart 2 represents the duration of diabetes in those not receiving insulin.

The number of known deaths of those who received insulin is 41. This represents a known mortality of 13.2 per cent of the total (301) that we have been able to follow. If those who have not been followed by us are all dead the maximum mortality increases to 20.5 per cent. The duration of diabetes in this group that have died varied from two days to fourteen years and seven months. This is shown graphically in chart 3, and attention is again called to the high mortality in the first month after diabetes developed.

TABLE 7.—*Analysis of Fifty-Five Deaths*

Patient	Sex	Age at Onset Yr.	Age at Onset Mo.	Year of Death	Duration of Diabetes Yr.	Duration of Diabetes Mo.	Cause of Death	Comment
				Before Insulin				
1. LB	M	5	..	1917	2	6	Unknown	
2. BT	M	5	3	1921	..	—1	Coma	None; first seen in coma
3. RN	M	6	1	....	..	—1	Coma	None; first seen in coma
4. AB	F	4	2	1922	2	2	Ketosis	Gangrene of nose
5. JM	M	1	6	....	..	—1	Coma	None; first seen in coma
6. DS	M	2	11	....	..	—1	Coma	None; first seen in coma
7. HFB	M	9	4	....	2	1	Pneumonia	None
8. GY	F	9	6	....	7	..	Influenza	None
9. DS	M	7	1	....	..	—1	Coma	None; first seen in coma
10. LL	F	10	..	....	2	8	Coma	None
11. HH	M	7	..	....	..	—1	Coma	None; first seen in coma
12. LF	F	10	..	....	..	—1	Coma	None; first seen in coma
13. TG	M	7	9	....	..	—1	Coma	None; first seen in coma
14. WC	M	12	..	....	6	..	Coma*	Infection of upper respiratory tract
				After Insulin				
15. EB	M	3	1	1923	5	7	Myocardial failure	Sudden myocardial death following diphtheria with laryngeal obstruction
16. GV	F	8	11	....	..	—1	Coma	Pneumonia
17. AG	M	7	..	....	5	7	Pneumonia*	None
18. KE	F	3	1	1924	..	5	Coma	Severe enteritis
19. LJ	F	4	1	....	..	11	Unknown†	
20. AM	M	15	..	1925	1	..	Coma†	Stopped insulin; operation done; diabetes not cared for
21. JP	F	3	..	1926	4	..	Unknown†	
22. BH	M	3	6	....	2	11	Diphtheria	None
23. WM	M	2	5	....	..	6	Pneumonia	Empyema
24. EW	M	4	5	1927	..	—1	Coma	Record indicates inadequate treatment
25. HH	F	2	6	....	..	—1	Hypoglycemia*	Overtreated
26. BC	F	11	6	....	2	2	Coma†	Appendectomy done; no attention to the diabetes
27. GJ	F	4	1	1928	1	6	Coma*	Acidosis almost cleared when patient died suddenly; no cause found at autopsy
28. WA	M	10	6	....	..	8	Coma†	Parents refused to allow diet and insulin
29. AMT	F	7	10	....	..	—1	Coma	Record indicates inadequate treatment
30. NJ	F	8	3	....	..	—1	Coma	Record indicates inadequate treatment
31. TC	M	11	1	....	1	2	Lymphosarcoma*	None
32. BA	M	9	..	1929	3	11	Coma	Lateral sinus thrombosis
33. JL	F	14	..	....	5	9	Influenza	Ketosis
34. AP	M	4	6	1930	4	2	Pertussis*	
35. RI	M	4	..	....	..	—1	Coma*	Otitis media
36. FC	F	8	2	....	8	..	Unknown†	
37. RF	F	11	..	....	5	6	Unknown†	
38. LW	F	6	9	1931	7	..	Cerebral embolus	Abscess of lung
39. RS	M	7	5	....	1	..	Coma*	Record indicates inadequate treatment
40. RR	M	5	10	1932	4	..	Coma*	Stopped insulin; coma; treatment delayed; moribund on admission
41. BMcR	F	1	5	....	..	—1	Coma*	Pneumonia; hyperpyrexia
42. FH	M	1	10	....	..	6	Coma	Stopped insulin; coma; treatment delayed; died before any treatment was given
43. ES	M	11	4	....	1	6	Drowning	
44. MH	F	7	9	1933	5	8	Coma*	Hyperpyrexia
45. RB	M	1	6	1934	1	4	Thrombosis of lateral sinus	Flexner's dysentery; acute nephritis
46. CJ	M	6	10	....	..	—1	Coma*	Gangrene of small intestine with peritonitis possibly due to large doses of castor oil before admission
47. JL	F	..	2	1935	..	—1	Acute pancreatitis*	Ketosis; hyperpyrexia
48. MF	F	9	..	....	11	10	Coma*	Treatment delayed
49. PD	F	9	6	....	2	7	Coma*	Stopped insulin; treatment delayed; pneumonia; herniation of cerebellum; edema of lungs; fatty liver; hyperplasia thymus
50. RZ	M	9	9	1936	1	6	Pulmonary tuberculosis*†	Tuberculosis of spine
51. DS	F	7	8	....	..	—1	Pneumonia*	Pyelitis; renal abscesses; acute hepatitis; fatty liver
52. JS	F	14	9	....	5	2	Coma†	Treatment delayed
53. RS	M	12	11	....	2	10	Head injury*	Cerebral thrombosis; pulmonary embolism; acute cystitis; hepatomegaly
54. AJ	F	9	..	1937	14	1	Pneumococcic meningitis*	Pneumococcic pneumonia; pneumococcic otitis media; petrositis
55. BJ	F	3	..	....	1	6	Coma*	Stopped insulin; coma; treatment delayed; moribund on admission; bronchopneumonia (terminal)

* Autopsy.
† Did not die under our care.

We have subdivided the fifteen years of our experience with insulin into three five year periods (table 8).

The steady improvement in the mortality rate and the duration of disease in the patients who have died was modified partly by the constant addition of new patients who had been exposed to the hazards of diabetes

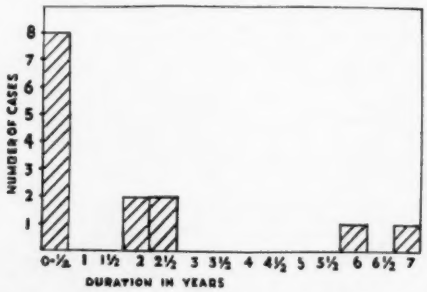

Chart 2.—Duration of diabetes in 14 patients who died. These patients received no insulin.

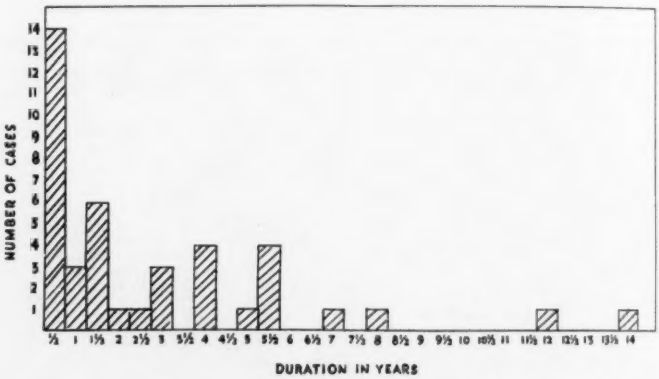

Chart 3.—Duration of diabetes in 41 patients who died. These patients were treated with insulin.

for a shorter period, but we believe it also indicates earlier diagnosis and more adequate treatment.

Of particular interest are 86 children in whom diabetes developed prior to January 1928 and for whom insulin was available, that is, those who had an opportunity to live ten years or more. Twenty-one, or

approximately 25 per cent, have died; only 3 of the deaths have occurred since 1930. For those exposed less than ten years the mortality has been 9.2 per cent.

CAUSES OF DEATH

Inquiry into the causes of death in this entire group shows that 61.8 per cent of the deaths must be attributed directly to diabetes. The highest mortality was naturally in the group treated before insulin was available, in which 79 per cent died as a result of diabetes but we must admit that even in the period during which insulin was given there was no other adequate cause for 57 per cent of deaths. These figures are based on the total known causes of death, but the actual cause of death was unknown in 5 instances. In table 7 are listed the causes of death in both periods.

In the period before insulin was available, 10 of the deaths from diabetes were due to uncomplicated coma and 1 to severe acidosis with gangrene of the nose and malnutrition. In the period during which

TABLE 8.—*Fifteen Years' Experience with Insulin*

Period	New Patients	Patients Held Over	Total	Total Known Deaths	Average Duration of Diabetes, Years
January 1923 to January 1928.....	67	11	78	12 (15.4%)	1.9
January 1928 to January 1933.....	126	66	192	17 (8.8%)	2.6
January 1933 to January 1938.....	123	175	298	12 (4.0%)	3.8

insulin was given 21, or approximately 50 per cent, died in coma. There was 1 death due to hypoglycemia and 1 to acute pancreatitis and ketosis. In 13 cases of diabetic coma there were no complications, but in 6 of these the insulin treatment was stopped or refused, and in 2 treatment was delayed until too late, in 1 case by the parents and in the other owing to delayed diagnosis. Four charts gave definite indication of inadequate treatment, and in 1 instance the treatment seemed adequate but sudden death ensued after the acidosis had cleared, the cause of which was not determined even at autopsy. In the other 8 cases of coma there was a severe complication, such as pneumonia in 3 instances, severe enteritis in 1, thrombosis of the lateral sinus in 1, otitis media in 1, hyperpyrexia in 1 and gangrene of the bowel with peritonitis in 1 (possibly the result of huge doses of castor oil administered by the parents before admission).

What we may call nondiabetic deaths during the period of administration of insulin include 3 due to pneumonia, 1 to myocardial failure after diphtheria, 1 to diphtheria, 1 to lymphosarcoma, 1 to influenza, 1 to pertussis, 1 to cerebral embolism, 1 to drowning, 1 to thrombosis

of the lateral sinus, 1 to pulmonary tuberculosis, 1 to injury to the head and 1 to pneumococcic meningitis. In all of these instances the diabetes was under satisfactory control at the time of death.

DURATION OF DIABETES IN THE LIVING

In the group of patients living at the time of writing (260) we eliminated all those in whose cases the disease was of less than six months' duration. The longest duration was seventeen years and seven months. The duration by years is presented in chart 4.

Two hundred and twenty-five (86.5 per cent) of these children have had diabetes for two years or over. This was about the average duration

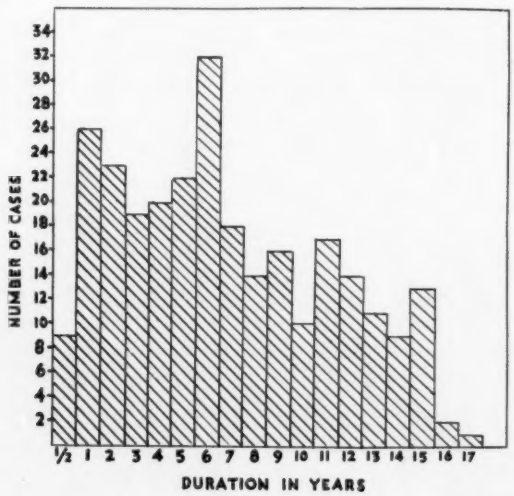

Chart 4.—Duration of diabetes in 260 patients living at the time of this report.

of life prior to the use of insulin. In table 9 we have listed the duration in years in relation to the total number in each year group. It is interesting to note that 62.7 per cent have a duration of five years or over, 25 per cent of ten years or over and 5.4 per cent of fifteen years or over.

NONFATAL COMPLICATIONS

There is perhaps no better way to evaluate the hardihood of these diabetic youngsters and the efficiency of present day treatment than to consider the complications which have been successfully met during the course of the diabetes (table 10). Seventy-three children have survived

TABLE 9.—*Duration of Diabetes*

Duration	No. of Patients
6 months or over	260
1 year or over	251
2 years or over	225 (86.5%)
3 years or over	202
4 years or over	183
5 years or over	163 (62.7%)
6 years or over	141
7 years or over	109
8 years or over	91
9 years or over	79
10 years or over	65 (25%)
11 years or over	57
12 years or over	42
13 years or over	30
14 years or over	21
15 years or over	14 (5.4%)
16 years or over	3
17 years or over	1

TABLE 10.—*Nonfatal Complications*

Complicating Factors	No. of Cases	Complicating Factors	No. of Cases
Ketosis	131	Tuberculous adenitis	1
Coma	73	Hilus tuberculosis (roentgen)	1
Measles	38	Adenitis	3
Mumps	14	Ichthyosis	1
Chickenpox	25	Parotitis (nonspecific)	1
Infection of upper respiratory tract	105	Anemia	1
Pertussis	19	Concussion	1
Pneumonia	7	Burns with skin grafting	2
Smallpox	0	Poliomyelitis	1
Scarlet fever	4	Herniotomy	1
Diphtheria	3	Fracture of leg	2
Tonsillitis	46	Fracture of spine	1
Tonsillectomy	43	Pregnancy (18 pregnancies)	12
Obesity	48	Abortions	5
Constipation	4	Cesarean sections (7 operations)	6
Appendicitis	12	Gonorrheal vaginitis	1
Appendectomy	9	Conjunctivitis	1
Allergy	8	Paronychia	1
Gangrene of nose	3	Mastoiditis	1
Nutritional edema	1	Mastoidectomy	1
Enteritis (1 castor bean)	25	Edema (cause unknown)	2
Tracheotomy	1	Jaundice (catarrhal)	2
Furunculosis	15	Cystitis	2
Cellulitis	5	Pyelitis	3
Typhoid fever	1	Diphtheria carrier	4
Enlarged liver (no jaundice)	5	Pleurisy	1
Enlarged liver (jaundice)	1	Abscessed teeth	2
Cirrhosis of liver	1	Ovarian cyst, with removal	1
Needle removed	1	Tapeworm	1
Antrotomy	1	Retinitis	2
Hypoglycemia (1 with hemiplegia)	5	Cataracts	1
Periods of spontaneous hypoglycemia	1	Pilonidal cyst	1
Traumatic rupture of spleen	1	Pelvic inflammation with peritonitis	1
Operation for squint	1	Impetigo	1
Hypothyroidism	3	Renal abscesses	1
Vincent's angina	1	Cholecystitis	1
Dental caries	9	Roundworms	1
Food poisoning	1	Neuritis	1
Scabies	2	Hysterectomy	1
Pulmonary tuberculosis	1	Arteriosclerosis	1

coma, 33 on more than one occasion. One child was admitted to the hospital twenty-one times; in each instance the diagnosis of diabetic coma was made. (This patient is now married and has a daughter 3 years of age.) One hundred and thirty-one patients had ketosis of sufficient severity to require energetic treatment, 40 on more than one occasion.

Retinitis was observed in only 2 patients, both females. In 1 it developed during pregnancy. Cataract was observed only once. There was only 1 instance in which clinical evidence of arteriosclerosis was present. The incidence of tuberculosis was remarkably low.

Of all the complications the most interesting and probably the most significant was pregnancy. Prior to the period during which insulin was given girls having diabetes before the sixteenth year did not live long enough, as a rule, to marry. Sexual development was delayed, and total amenorrhea was the rule rather than the exception.

TABLE 11.—*Present Diets by Food Values*

Present Age	No. of Cases	Carbohydrate			Protein			Fat		
		Maximum	Minimum	Average	Maximum	Minimum	Average	Maximum	Minimum	Average
0-3	4	150	130	140	60	50	55	110	60	82.5
4-6	8	150	120	134.5	60	50	57.4	90	70	81.2
7-9	26	220	135	147.2	85	60	65.5	120	60	93.6
10-12	41	220	130	163.7	90	60	70	140	50	96.7
13-15	31	250	125	175.4	100	65	76.9	125	50	104
16-18	45	290	120	173.1	100	60	74.5	150	35	98
19-21	13	210	130	160.7	105	65	75.4	120	35	83.3
22-24	15	250	130	169.3	95	60	73	130	60	96.3
25-27	3	180	140	166.6	80	60	72	90	80	83.3
28-30	3	160	60	123.3	70	60	63.3	120	65	91.7

A new generation has been added to medical history. These girls are beginning to marry and have children. In this group there were eighteen pregnancies in 12 women. Seven cesarean sections were performed on 6 women. There were five abortions, one of which was induced because of intractable ketosis and vomiting before the patient came under our care. In another case hysterectomy was done at the time of the abortion. The other abortions were spontaneous. One child died at birth. There was no maternal mortality.

DIETS

In planning diets we have not been particularly concerned about any definite ratios between carbohydrate and fat or between the total available dextrose and fatty acids. Our attention has been given primarily to adequate nutrition and growth for each patient. This obviously implies adequate protein, vitamins and minerals as well as adequate calories.

We believe that the improvement noted among children with diabetes during the past decade can be attributed almost entirely to more nearly

normal nutrition rather than to any particular dietary scheme. As the amount of carbohydrate allowed tends to exceed approximately 100 Gm. a day the content of accessory factors automatically tends toward optimal values. Also, as carbohydrate is increased fat is automatically decreased if the caloric value of the diet is maintained at the same level.

Table 11 gives the food values of the diets with the averages for each in the various groups based on present age grouped by three year periods.

INTELLIGENCE TESTS

Intelligence ratings have been made of 62 unselected children in this group. At the time of the first test the average intelligence quotient was 105.4, standard deviation 11.7 $\pm$ 0.89. The intelligence quotients of the children in this group were well in advance of the normal distribution for unselected children as indicated by intelligence quotients above 110 (42.1 per cent), from 90 to 110 inclusive (47.4 per cent) and below 90 (10.5 per cent). Terman's normals for unselected children are as follows: above 110, 20.6 per cent; 91 to 110, 60 per cent; and below 90, 19.4 per cent.

SUMMARY

The statistical data in 341 cases of juvenile diabetes are presented. No new theories or principles have been developed in the course of the study. The purpose has been to add to the accumulating data on the various phases of juvenile diabetes.

HYPERTHERMIA, GENUINE AND SPURIOUS

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Richet,[1] in his monograph on animal heat, tabulated 109 examples of hyperthermia in man with temperatures ranging from 42 to 44.6 C. (107.6 to 112.2 F.). There were 13 survivals in this group. He rejected as unreliable several reported observations of temperatures from 44.1 to 50 C. with recovery and expressed unwillingness to accept as valid any observation of temperature above 46 C. (114.8 F.). This decision was based not merely on clinical studies but on extensive physiologic experimentation and observations on various mammals. Hombourger[2] defined fever as a morbid state resulting from exaggeration of proteolysis and disturbance of the heat-regulating mechanism, and he designated as hyperthermia a high elevation of temperature, whatever the cause. A fever with a temperature above 41 C. (105.8 F.) he designated as "hyperthermic fever." This author expressed agreement with Richet. He mentioned the famous cases of Jacobi and of Heber Jones, as well as the patient of Du Castel,[3] who by tapping the upper end of the thermometer succeeded in registering a temperature above 160 C. (320 F.). He added the caustic remark that in France one exercises reserve in reporting cases of this sort, contrary to the custom in certain countries. He tabulated 33 cases of hyperthermia reported in the literature since Richet and added 1 new case of his own, in which the maximum temperature was 44.2 C. (111.6 F.), with recovery.

The clinical reports of hyperthermia may be grouped into different classes: (1) instances of proved trickery in which the thermometer has been caused to register a high temperature by artificial means not related to body heat, (2) instances of suspected trickery not clearly proved, (3) hysterical fever, (4) hyperthermia originating in disturbance of the central nervous system, (5) hyperthermia of heat stroke, (6) therapeutic hyperthermia, (7) fever of disordered metabolism and intoxications, (8) fever of infectious disease and (9) hyperthermia of complex causation.

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1. Richet, C.: La chaleur animale, Paris, Félix Alcan, 1889.
2. Hombourger, P.: Les fièvres hyperthermiques, Thesis, Paris, no. 126, 1919.
3. Du Castel: Simulation thermique chez une hystérique, Bull. et mém. Soc. méd. d. hóp. de Paris **1**:174 (April 25) 1884.

Hyperthermia of Trickery.—Some of the classic examples of fraudulent hyperthermia are worthy of brief mention. Early in 1880, Little [4] observed a woman aged 23 years in the Adelaide Hospital, Dublin, Ireland, who had fallen on the back of her head some days before. On April 19 her axillary temperature registered 115 F., and the same reading was obtained at 5 a. m. on April 20. A few hours later the Fahrenheit thermometer registered 99.4. On Monday, April 26, a temperature of 125.5 F. was recorded, and later the temperature was 127 F. on two occasions. Subsequently it reached 130.8 F. Late in May the patient appeared to be convalescent. Mackenzie,[5] in a letter to the medical publication in which the case had been reported, suggested to Little that he take the temperature always with two or more thermometers simultaneously. Mackenzie [6] himself was at that time observing a woman at the London Hospital, whose case was later reported to the Clinical Society. This patient was admitted Feb. 25, 1879, with a painful stump after amputation at the thigh in 1878. The temperature registered 108 and 111 F. on different occasions. After surgical revision of the stump she was discharged in August. She was readmitted on October 21, and another piece of bone was removed from the amputation stump. In January 1880 there were numerous recordings of temperatures between 108 and 114 F. and records of a temperature of 114.2 F. on January 16, 120.8 F. on January 22, 116.6 F. on January 23 and 116.8 F. on January 26. The patient was readmitted on August 16, and the thermometer again registered high temperatures. Simultaneous records with two or more thermometers were inconsistent; two instruments in the same axilla registered 105.5 and 101 F. respectively, and simultaneously with an oral and rectal temperature of 98.6 F. the axillary temperature was 104.6 F. Later the patient confessed that she had applied poultices and hot water bottles to the thermometers. Mahomed,[7] in the discussion of this case, reported a similar one, in which the patient was able to produce all sorts of variations in the readings, from normal to 120 F. At one time simultaneous records with three instruments gave readings of 107 F. in the mouth, 102 F. in one axilla and 114 F. in the other axilla. Once a reading of 128 F. was recorded. The patient's technical method was never discovered. Newnham,[8] who

4. Little, J.: Case of Hyperpyrexia in Adelaide Hospital, Dublin, M. Times & Gaz. **1**:457 (April 24); 482 (May 1); 510 (May 8); 585 (May 29) 1880.

5. Mackenzie, S.: Abnormally High Temperatures, M. Times & Gaz. **1**:620 (June 5) 1880.

6. Mackenzie, S.: A Case of Excessively High Temperatures, Lancet **2**: 796 (Nov. 5) 1881.

7. Mahomed, F. A.: A Case of Excessively High Temperatures, Lancet **2**: 796 (Nov. 5) 1881.

8. Newnham, W. H. C.: Hyperpyrexia, Lancet **2**:894 (Nov. 19) 1881.

served as medical ward clerk and observed the patient closely from Dec. 1, 1879 to Feb. 28, 1880, was at first skeptical but was eventually convinced that the high temperatures of this patient were genuine. With his fingers in the axilla and without the slightest friction against the thermometer he observed temperatures of 109 and 111 F. The skin felt burning hot. It seems, therefore, that this patient may have had genuine as well as fraudulent hyperthermia.

Galbraith,[9] in 1891, reported the "Omaha case." The patient was a married woman aged 26. She was thought to have an abdominal pregnancy. Many fragments of bone (over 1,000) were removed from her vagina and rectum from time to time, which later were found to be bones of birds and mammals (chicken, mutton or beef bones). Temperatures of 112, 96, 107, 125, 145, 117, 145 and 98 F. were recorded. At one time a temperature of 112 F. was recorded simultaneously by two thermometers, one beneath the tongue and one in the axilla, but it seems that 112 F. was the uppermost limit of the columns. With special thermometers, simultaneous readings at one time were 145 F. in the axilla and 125 F. beneath the tongue. Half an hour later the temperature was 98 F. With every precaution to detect fraud, with the patient nude and sitting in a chair, simultaneous observations of the temperature in the axilla and under the tongue were 137 and 131 F. respectively. On another occasion the axillary temperature was recorded as 131 F. while the temperature simultaneously registered in the popliteal space was below normal. The highest temperature observed by the physician was 151 F., but the hospital nurse made one record of 171 F. The fraudulent character of this patient was later exposed by Summers [10] and Poe,[11] but they were not able to elucidate the technic by which the remarkable thermometric records had been produced. Apparently hot water was sometimes employed, but this could hardly explain the observations of Galbraith.

Jones,[12] in 1891, reported the case of a girl aged 14 whose temperature on various occasions had been recorded as 108, 109, 114, 97, 114, 115, 115, 135, 150, 156 and 99.5 F. When this patient was seen by Holder, she was able to produce apparent axillary temperatures of 98, 103, 114.4 and 97 F. within a few minutes. The girl was an athlete and a contortionist, but her technic for causing high thermometric

9. Galbraith, W. J.: A Remarkable Case, J. A. M. A. **16**:407 (March 21) 1891.

10. Summers, J. E.: Omaha's "Remarkable Case" of High Temperature: An Undoubted Hysterical Fake, Omaha Clin. **4**:115 (Sept.) 1891.

11. Poe, C. T.: A Chronic Malingerer, Omaha Clin. **4**:269 (Feb.) 1892.

12. Jones, H.: A Case of Wonderful Temperature, Memphis M. Month. **11**: 252 (June) 1891; High Temperature, 150° F., ibid. **11**:445 (Oct.) 1891.

readings has not been explained. Jones considered her to be free from guile and trustworthy in every respect.

Jacobi,[13] in 1895, presented before a distinguished audience his report of a man aged 29 observed at the German Hospital, New York, in January 1893. The temperatures of this patient had been recorded as 111, 112, 113.4, 117, 118, 123, 135, 131, 136, 133, 124, 148, 136, 137, 148, 135, 132, 135, 142, 148, 115.8, 113, 109.8, 143.8, 142, 125 and 132 F. A few days later (March 13) he stole away from the hospital. In the discussion of this case, William H. Welch expressed himself as completely skeptical of the trustworthiness of the observations; George Dock asked about the temperature of the freshly voided urine (which had not been tested); William Osler asked about the heat of the abdominal skin. Jacobi, however, insisted that his observations represented facts.

With all due respect for the skill and integrity of the observers, one must share the total skepticism of Welch in regard to the validity of these recorded observations of the temperature of the human body. One must therefore consign these examples to the first two of the aforementioned classes of hyperthermia, namely, instances of proved trickery or of suspected trickery not clearly proved, in which the high thermometric readings are evidently not related to body heat.

The technical methods by which false high thermometric readings (fever of the thermometer) may be produced have not been fully elucidated. When the patient has access to a hot water bottle, a steam pipe near the bed or some other source of external heat, this would seem to offer the simplest means of forcing up the column in the thermometer. No especial skill is required to accomplish this result. Another trick depends on friction. If one holds the thermometer shaft parallel to the index finger with the bulb firmly pressed into the ball of the finger and then rubs this bulb and the adjacent finger tissue vigorously with firm pressure on a taut piece of cloth, one will quickly sense the increased temperature in the finger, and the column in the thermometer may be caused to record a high temperature. This can be accomplished with one hand. Another technic, requiring slightly more skill and practice, consists in holding the thermometer with the bulb tightly pressed between the thumb and the forefinger while the forefinger is vigorously rubbed up and down on the thumb and on the compressed thermometer bulb. Another procedure depends not on heating the thermometer but on displacement of the column of mercury by mechanical jarring. By vigorously snapping the upper end of the thermometer with the finger or thumb so as to drive the glass toward the bulb, one may displace the column of mercury toward the top of

13. Jacobi, A.: Hyperthermy in a Man up to 148° F. (64.4° C.), Tr. A. Am. Physicians **10**:158 (May) 1895.

the instrument. The mercury column may become separated (broken column) so that there are vacant spaces in it along the shaft, but when one has developed sufficient skill it is possible to get the mercury up to a high level without a break in the column. Such tapping may be accomplished with one hand if the bulb of the instrument is held in the mouth, the axilla, the rectum or the vagina. The procedure requires some technical skill, and a noise is produced by the tapping which may be heard by a patient in the neighboring bed. The height of the reading attainable by this method is limited only by the length of the capillary of the instrument. One may also displace the mercury upward by swinging the thermometer in a narrow arc with the bulb nearer the center of rotation, a manipulation just the reverse of that used to throw down the mercury column before use. This trick nearly always produces a broken column of mercury. With experimentation and practice I have become reasonably adept in these technical procedures.

Other fraudulent tricks are suggested in the literature on hyperthermia. Mahomed stated that one may produce a high reading by wrapping the thermometer bulb in silk, inserting it in the mouth, inhaling through the nose and then exhaling through the mouth. I have not been able to confirm this. It has been suggested also that muscular movement may produce heat of friction in the axilla so as to cause a fraudulent high reading and that one may rub the thermometer bulb with the tongue or produce friction by rapidly repeated contraction of the sphincter muscles so as to give rise to fraudulent high readings for oral or rectal temperatures. I have entirely failed to confirm these suggestions even after the expenditure of considerable effort. Of course, a special technical skill may be involved, which I have failed to master.

In order to avoid deception by these or other tricks, the physician may have recourse to multiple simultaneous observations of the temperature. One or more thermometers may be placed in each axilla, another beneath the tongue and another in the rectum, the stem of each instrument being held steadily by the hand of an observer and never entrusted to the patient. Reasonable agreement of the readings would indicate reliability, while a marked variation shown by one or more of the thermometers would point to error or fraud. The temperature of the freshly voided urine and feces should also be observed.

Hysterical Fever.—The recognition of hysterical fever and hyperthermia originating in disturbance of the central nervous system is justified in part by animal experimentation. Richet by passing a needle into the brain of the rabbit was able to cause a rise in temperature from 39.2 C. (102.6 F.) to 42.5 C. (108.5 F.) without other recognizable alterations in behavior of the animal. He was unable to

recognize a localized "heat center," however, and even today there is no certain agreement in regard to the exact portions of the brain concerned with this phenomenon. Examples which may be tentatively assigned to these categories are not wanting in the literature.

Crouzet [14] accepted hysterical fever as a definite entity, distinct from the hyperthermia of trickery, or fever of the thermometer. He reviewed in considerable detail numerous examples of this condition described in the literature previous to 1895. Nearly all of the patients were women with other manifestations of hysteria. The temperature curves were extremely variable, and as a rule the physical well-being of the patient was remarkably good considering the temperatures recorded. Crouzet attempted to classify the conditions under such headings as (1) hysterical fever proper and (2) hysterical fever with visceral pseudodisease, that is, pseudotyphoid, pseudomeningitis, pseudo disease of the lung, pseudoperitonitis or pseudomalaria. However, he considered such a classification premature.

The manifestations of hysteria present difficulties in differential diagnosis, and it seems probable that cases of the hyperthermia of trickery and hyperthermia associated with genuine gross organic disease of the central nervous system have been reported from time to time as examples of hysterical fever. The lines dividing the three classes of hyperthermia may therefore be considered as not sharply defined.

Soulier [15] has recorded an example of hyperthermia apparently best designated as hysterical fever. The patient, a delicate woman, after a serious disappointment on Sunday morning fell into a narcoleptic state. She was absolutely insensible. The following night her temperature (axillary and vaginal) reached 44 C. (111.2 F.). On Monday and on Tuesday the temperature reached the same level. The patient recovered on the fifth day without memory of the events preceding the trance. The profound slumber resembled chloroform narcosis. Deception seems to have been reliably excluded in this case.

A more recent example of hysteria or of trickery has been recorded by Lhermitte and Aman-Jean,[16] and it illustrates the difficulty of distinguishing the two. The patient, a woman aged 44, received several applications of radium to a carcinomatous uterine cervix. On May 23 (1936) she had severe chills and violent hallucinations, and the temperature of 43 C. (109.4 F.) was recorded by three thermometers. For seven days the rectal temperature was between 40 and 43 C. (104

14. Crouzet, M.: La fièvre hystérique, Thesis, Paris, no. 10, Paris, G. Steinheil, 1895.

15. Soulier, H.: Hyperthermie apyrétique corrélative avec état narcoleptique, Lyon méd. **93**:5 (Jan. 7) 1900.

16. Lhermitte, J., and Aman-Jean, F.: Hyperthermie et pithiatisme: La fièvre du thermomètre, Rev. neurol. **67**:206 (Feb.) 1937.

and 109.4 F.). At 7 a. m. on May 30 she was given a capsule of methylthionine chloride (methylene blue) and was told that if her urine became blue she would experience a severe chill and would then recover. At 10 p. m. there was a violent chill; the urine was blue, and the temperature at 6 a. m. on May 31 was normal. There was no more fever, and the patient was discharged June 6. Great care was exercised to prevent fraud. While the thermometer was in the rectum there was no movement of the thighs; nevertheless, the authors concluded that the temperatures were fraudulent and recognized that some persons possess extraordinary talents (out of all proportion to their mediocre or inferior intelligence) for trickery which even the most scrupulous observers may not detect. The hyperthermia in this case might be considered by some as hysterical fever.

Hyperthermia Referable to the Central Nervous System.—Hyperthermia in association with severe trauma or infectious lesions of the brain or of the upper part of the cervical portion of the spinal cord has been repeatedly observed. In many instances there can be no ground for suspicion of fraud because of the desperate condition of the patient, who may even be in coma. Brodie,[17] in 1837, seems to have reported the first example, the case of a man with a fatal fracture of the cervical portion of the spine, with a temperature of 43.9 C. (111 F.). Macgregor[18] observed a man aged 76 in terminal coma apparently due to cerebral hemorrhage, with an axillary temperature of 109 F. three hours before death. Massey and Carter[19] recorded terminal hyperthermia in a man aged 27, in whom an abscess of the brain developed two days after mastoidectomy with an axillary temperature of 108.6 F. shortly before death. Macewen[20] reported the case of a youth aged 19 with a cerebellar abscess, who showed a temperature range from 104 to 108 F. on the day of his death. Many similar examples have been reported.

Hyperthermia of Heat Stroke.—Hyperthermia of heat stroke or sunstroke not uncommonly reaches a temperature of 110 F. or above. Osler stated on the authority of F. A. Packard that 31 patients with sunstroke were admitted to the Pennsylvania Hospital in the summer of 1887, and the temperature of the majority was between 110 and

17. Brodie, B., cited by Hambourger.[2]

18. Macgregor, D.: A Case of Hyperpyrexia with Coma, Brit. M. J. **1**:1199 (May 16) 1896.

19. Massey, A., and Carter, H. S.: Terminal Hyperpyrexia, Brit. M. J. **2**: 922 (Nov. 11) 1922.

20. Macewen, W.: Pyogenic Infective Diseases of the Brain and Spinal Cord, Meningitis, Abscess of Brain, Infective Sinus Thrombosis, Glasgow, James Maclehose & Sons, 1893.

111 F. Muscular activity without adequate dispersion of heat from the body would seem to be important in this condition.

Therapeutic Hyperthermia.—Therapeutic hyperthermia represents a relatively recent development. It may be induced by infection (malaria), by intoxication (typhoid vaccine), by bactericidal or bacteriostatic chemicals, by bacteriophage, by application of external heat or by use of other forms of radiant energy. Because of the practical application of these measures in the treatment of disease conditions, a rather voluminous literature relating to them has already accumulated, and active investigations are in progress. A review of these artificially induced fevers would lead beyond the scope of the present paper.

Fever of Disordered Metabolism and Intoxications.—Of the metabolic fevers, perhaps the best known is that associated with exophthalmic goiter, in which disease there is a definitely demonstrable overproduction of body heat as the result of excessive oxidation. However, the temperature in this disease does not ordinarily approach the level of hyperthermia. Drug intoxications may be associated with elevated temperature. In strychnine poisoning the muscular spasms lead to increased heat production. Other poisons, such as aconitine, colchicine, digitaline and especially veratrine, have been found to induce high temperatures (45.6 C., or 114 F.) in dogs. Richet and (later) Hombourger have reported experimental observations in this category.

Fever of Infectious Disease.—Elevation of body temperature associated with active infection is so common that the casual observer often considers one the necessary companion of the other, and some would maintain that elevation of temperature in infection constitutes the only genuine fever, all other examples of increased temperature being placed by them in other categories. Very high temperatures have been observed, especially in cases of scarlet fever, rheumatic fever, pneumonia, malaria, tetanus, typhoid fever, abscess of the liver, meningitis, puerperal sepsis and other bacteremias. When, however, the temperature reaches the level of hyperthermia (41 C. or 105.8 F.) one is inclined to consider the infectious fever as dangerous to life itself. Probably physicians have been accustomed in the past to ascribe too great importance to high temperature when, in fact, the danger is due to other disturbances of which the temperature is merely one manifestation.

Hyperthermia of Complex Causation.—Under this caption should be mentioned examples of infectious fever in which further increase of temperature is induced by therapeutic measures, such as the use of typhoid vaccine for chorea, external heat for rheumatic fever and injection of mercurochrome and therapeutic serum or bacteriophage for septic conditions (Hugh Young reaction). One also includes examples

in which the patient, having had a fever due to infection, finds it convenient and profitable to perpetuate the kindly care by production of fraudulent high temperature readings. One easily visualizes the successive stages of this condition, which may eventually be terminated by detection of fraud.

SUMMARY

1. Temperatures above 46 C. (114.8 F.) in man should generally be considered the result of fraud or trickery and are not to be accepted without more convincing proof than has, so far, been presented in any instance.

2. Temperature readings between 41 C. (105.8 F.) and 46 C. (114.8 F.) properly designated as hyperthermia, should be accepted as valid only after the most careful scrutiny of the evidence in each case.

3. Some of the technical tricks for producing false temperature readings have been exposed and safeguards against deception indicated.

4. Apparently there is a genuine hyperthermia of hysterical origin, and certainly there is hyperthermia due to lesions of the central nervous system, to heat stroke, to intentional application of excessive external heat and other therapeutic thermic procedures, to intoxications and to infectious diseases.

PROLONGED HYPERTHERMIA

REPORT OF A CASE WITH NECROPSY

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Examples of temperatures of 45 C. (113 F.) in man are sufficiently uncommon to deserve careful study and report, and examples of temperatures above 40 C. (104 F.) persisting for several weeks at this level are also unusual. At times, patients with such temperatures have been made the subjects of undesirable publicity. They present problems which are not yet completely elucidated. Osler,[1] in 1909, said:

> It is a suggestive fact that the cases of paradoxical temperatures reported of late years, in which the thermometer has registered 112° to 120° or more, have been in women. Fraud has been practised in some of these, but others have to be accepted, though their explanation is impossible under our known laws.

This statement still holds true in 1939. For these reasons the following case report is presented in considerable detail.

REPORT OF CASE

S. V., a white woman, was born in the United States on Dec. 24, 1911. Her father was killed in the World War. Her mother, two brothers and one sister were living and well. She had had measles and chickenpox. Otherwise she had been well until 1934, when, during her training as a student nurse, she had an attack of cholecystitis treated by cholecystectomy. Later, while employed as a graduate nurse in a hospital in Philadelphia, she had an infection in her left index finger, apparently due to a hemolytic streptococcus. She was treated at the Infirmary of the Philadelphia Hospital for Contagious Diseases on March 8, 1936 and subsequently. The finger was incised several times, and the distal phalanx was amputated. For a long time afterward the patient continued to have a temperature between 100 and 102 F. for which there was no evident cause. Later there developed abdominal pain, and she was sent to the Philadelphia General Hospital for study. There the finger was curetted, but it failed to heal, and on

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1. Osler, W., and McCrae, T.: The Principles and Practice of Medicine, ed. 7, New York, D. Appleton & Co., 1909.

August 6 a further amputation of the left index finger was performed. The patient did not make a satisfactory recovery; the fever continued, with pain in the right lower quadrant of the abdomen and vomiting. At this time, October 1936, there was no evidence of osteomyelitis of the stump. Roentgen study of the gastrointestinal series and of the colon after a barium sulfate enema gave negative results. A retrograde pyelogram of the right kidney at this time was normal. The lungs and heart were normal. Pelvic examination showed retroversion of the uterus but nothing to account for the fever. Repeated blood cultures gave negative results.

The eyegrounds were normal. The basal metabolic rate was —17 per cent. The patient was considered definitely hysterical and at times was suspected of having a psychosis. Psychiatric examination failed to confirm this. The temperature remained between 98.6 and 101 F. The red blood cell count remained near 4,000,000 and the hemoglobin at 80 per cent. The white blood cell count varied from 6.000 to 9,000, and the percentage of polymorphonuclear leukocytes was never above 56. On October 10 a partly obliterated appendix was removed, and the operation appeared to be without influence on the condition of the patient. After her return to duty the amputation stump of the left index finger remained tender, and from time to time there was a discharge of pus from sinuses which would close in the intervals. The first phalanx of the finger remained.

On June 9, 1937, the patient was again admitted to the Infirmary of the Philadelphia Hospital for Contagious Diseases, because of edema of the ankles and unexplained fever. The white blood cell count was 4,400, with 39 per cent polymorphonuclears. The temperature subsided, and the patient was discharged on June 18, still presenting an unsolved problem.

Late in 1937 she moved to New York city and was employed as a nurse at the Willard Parker Hospital and later (until March 1938) at the Hudson County Hospital in New Jersey. After April 1 she was employed in the women's surgical service at the New York Post-Graduate Medical School and Hospital. Because of the tenderness and intermittent opening of sinuses in the stump of the finger, she was admitted as a patient on June 21 for surgical revision of this stump, having remained on duty on June 20. At the operation at 5:49 p. m., June 21, with the patient under nitrogen monoxide and oxygen anesthesia, the old scar was excised. The distal half of the proximal phalanx of the left index finger was found softened and was removed with a rongeur down to the beginning of the articular flare. The wound was sutured, one rubber band being inserted for drainage. The operation was finished in six minutes. No record was made of microscopic or cultural examination of material removed at this operation.

The outstanding features of the subsequent record are shown in figure 1. On return from the operating room the patient was restless, threshing about in the bed and talking irrationally through the night. Side boards were placed on the bed at midnight. One-sixth grain (0.01 Gm.) of morphine was given at 9 p. m., and this dose was repeated at 1:30 a. m. The pain in the hand seemed beyond control. In addition, there was severe general itching, apparently unexplained. Her complaints were so out of proportion to the visible evidence of disease that she was considered hysterical. Sedatives were employed frequently every day. She was up in a chair on June 23, but on June 24 her pulse rate reached 130 and her temperature 100 F. On this date the following progress note was made: "The patient appears critically ill—dehydrated." On the next day the dressings were removed from the finger, and daily soaks of the hand in hot saline solution were instituted. On June 28 she walked to the bathroom, and on her return she became dizzy and fell to the floor, without evident injury. After removal of the drain, on June 29, she seemed more comfortable. On July 1 she tried to walk again

but was unsteady on her feet, and that evening she was depressed and had a prolonged weeping spell, eventually becoming quiet at 2:45 a. m. Itching of the skin returned on July 2. She was allowed to be out of bed on July 3 and 4, and her temperature had begun to rise. On July 5 a medical consultant discovered an icteric tint of the scleras and many petechiae, varying from pinpoint size to 2 mm. in diameter, over the anterior and lateral thoracic regions and slight tenderness in the right upper quadrant of the abdomen. According to the patient, the spots on the skin first appeared on July 2 and had appeared in crops since then. A blood culture was requested. On July 6 the icterus index of the blood was 18.8; the values for nonprotein nitrogen and dextrose were normal. Roentgen examination of the thorax gave negative results. Blood for culture was taken at 8:20 p. m., when the temperature had reached 104.4 F. The culture remained sterile. A blood count showed 3,210,000 red blood cells and 3,650 white blood cells per cubic millimeter, with 69 per cent polymorphonuclears. During the next few days there was persistent severe headache, for which an ice cap was used continuously. The patient was seen by various consultants, and the medical consultants agreed on a diagnosis of septicemia. The pain in the right upper quadrant of the abdomen continued and became more severe. A culture of blood taken on July 8 yielded on July 12 3 colonies of Staphylococcus aureus per cubic centimeter of blood. Meanwhile, on July 7, intravenous infusion of 5 per cent dextrose, 2 liters per day, was instituted, and a transfusion of 360 cc. was given on July 9. Exudate from the wound on the finger was taken for bacteriologic study on July 10, and Staphylococcus aureus was found in pure culture.

On July 11 blood was taken for culture at 1:45 p. m. The culture showed 44 colonies of Staphylococcus aureus per cubic centimeter of blood after twenty hours' incubation and 46 colonies per cubic centimeter of blood after incubation for ninety-six hours. At 1:47 p. m. on July 11 an intravenous dose of 2 cc. of stock asparagine staphylococcus bacteriophage was given and 8 cc. of the same phage was needled to the soft tissues of the suppurating finger stump. The patient's temperature rose to 106 F. at 8 p. m., and at 9 p. m. blood was taken for another culture, which remained sterile. In fact, all subsequent blood cultures, of blood taken on July 13, 15, 18 and 28, August 11 and 19, September 7 and 26 and October 4 and 7 remained sterile. When, however, the culture of blood taken at 1:45 p. m. on July 11 showed 44 colonies per cubic centimeter of blood on the following morning, it was decided to administer bacteriophage in a series of doses to induce a shock reaction. Intravenous injections were given as follows: 8:47 a. m., 2 cc.; 9:25 a. m., 3 cc.; 10:03 a. m., 5 cc.; 10:48 a. m., 7 cc.; 11:25 a. m., 10 cc.; 12:04 p. m., 13 cc.; 12:40 p. m., 15 cc.; 1:24 p. m., 20 cc.; 2:03 p. m., 25 cc.; 2:47 p. m., 30 cc.; 3:32 p. m., 30 cc.; and 4:16 p. m., 40 cc. This made a total of 200 cc. of the stock asparagine staphylococcus bacteriophage given intravenously in seven hours and twenty-nine minutes. The temperature was found to be 107 F. just after the last injection was given. At 5 p. m. it registered 108 F., and at 6 p. m. it was 110.2 F., with a respiratory rate of 42 and a pulse rate of 100. After an alcohol sponge the temperature was 108 F. (about 6:30 p. m.). The patient then had a chill lasting three minutes. At 7 p. m. the temperature was down to 104.2 F., and at 8 p. m. it reached its peak at 113 F. Several rectal thermometers were broken before it was possible to get one with a sufficiently long column. The skin was burning hot. The temperature observations were taken under the eye of a physician and are valid without question. A tepid sponge with 50 per cent alcohol was followed by temperatures of 108.4 F. at 9 p. m., 109.4 F. at 10:30 p. m. and 109.4 F. at 11 p. m. Rectal irrigation with ice water was proposed and was discarded as too dangerous. An intravenous infusion of 5 per

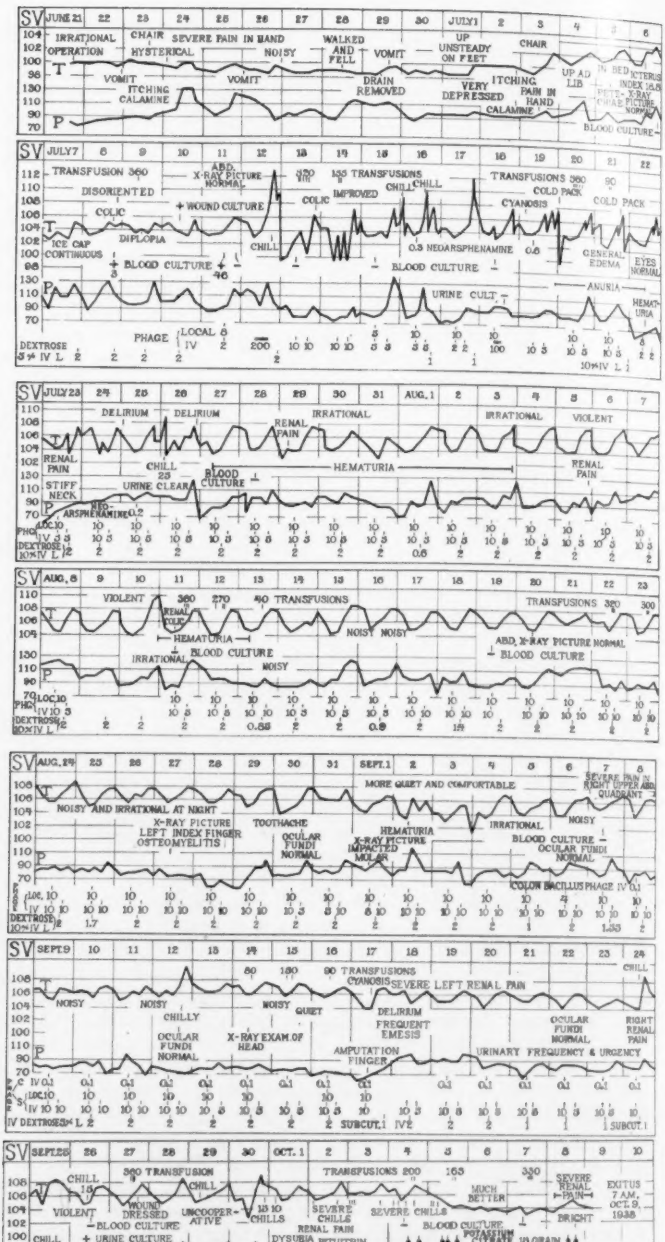

Fig. 1.—Abbreviated clinical record of S. V. The maximum temperature of 113 F. was reached on July 12, after intravenous injection of 200 cc. of staphylococcus bacteriophage in divided doses. There were anuria from July 19 to July 22 and hematuria from July 27 to August 3. Bacteriophage was administered intravenously and locally once or twice on almost every day, and dextrose solution in physiologic solution of sodium chloride was given intravenously, usually 2,000 cc. per day. The left index finger was disarticulated at the base of the first phalanx on September 17. After this there was aggravation of the urologic symptoms.

cent dextrose in saline solution at room temperature was started at 10:45 p. m., and at 11:30 this was chilled by application of ice bags to the infusion tube. A total amount of 2,000 cc. was given from 10:45 p. m. to 2:00 a. m. At midnight the temperature had come down to 99.4 F., and the infusion was allowed to proceed at room temperature. At 1:00 a. m. the patient's temperature was 99.6 F.; at 3:00 a. m., 102; at 4:00 a. m., 100, and at 6:30 a. m., 103. Catamenia began at 10:45 p. m., July 12, and there were complaints of pelvic cramps in the early morning of July 13, but the patient slept for a while after 11 p. m., and on the morning of July 13 she seemed none the worse for her extreme febrile reaction. Her blood pressure was 108 systolic and 75 diastolic. Transfusion of 520 cc. of citrated blood in divided doses (fractional transfusion) was given during the day and 155 cc. on July 14. The patient seemed distinctly better, but the temperature would not stay down. Bacteriophage by intravenous injection morning and evening was continued in 10 cc. doses, stock phage on July 13 and specific phage in 10 cc. doses on July 14; then reduced to 5 cc. doses on July 15 and 16 and to 2 cc. doses on July 17. The temperature rose to 112 at 8 p. m. July 17, suggesting that these smaller doses were inadequate.

On Monday morning (July 18) a progress note was made: "The patient appears bright. She seems tired but not exhausted. The heart sounds are rather weak and the pulse relatively slow. The blood pressure is 108 systolic and 78 diastolic. The relatively slow pulse with such high temperatures suggests a possible purulent lesion within the cranium. It seems certain that there are pyemic abscesses. Tenderness in the right side, over the upper pole of the right kidney, suggests that this may be one site of abscess. The liver seems not to be enlarged. The neck is not rigid." A series of doses of phage to a total of 100 cc. was given intravenously on this day.

Because of the persistent fever, intravenous injections of neoarsphenamine were given, 0.3 Gm. on July 16 and 0.6 Gm. on July 19. From 10 p. m. on July 19 to 11:30 a. m. on July 22, a period of about sixty hours, no urine was passed and percussion of the lower part of the abdomen did not reveal any dilatation of the bladder until near the end of the period. The urine passed naturally at 11:30 a. m. July 22 was red with blood. Ophthalmologic consultation on July 22, with careful examination of the fundi, revealed no evidence of abnormality. On July 23, however, the neck was slightly rigid, and a medical consultant recommended spinal tap, which was not done. Dextrose solution, 10 per cent in saline solution, was given daily, 2 liters every twenty-four hours, and the urine became free from blood on July 25. Another intravenous injection of neoarsphenamine (0.2 Gm.) was given on July 25. That night there was a chill lasting twenty-five minutes and a rise in temperature to 109 F. and from July 27 to August 3 there was always blood in the urine. It was decided to discontinue the arsphenamine.

A progress note on July 30, 1938, at 9:45 a. m. included the following data: "The patient appears bright and chatty, which is remarkable in consideration of her temperature. Her circulation is good. The urine passed at 5 a. m. contains red blood cells, about 20 per high power field in the fresh specimen. The absence of pus is remarkable and suggests that the blood may be due to something else than a renal infarct, possibly to a concretion or to diffuse toxic nephritis. One is therefore persuaded that the tenderness below the ribs in the back may be of hepatic rather than renal origin. Staphylococcus aureus was abundantly present in the specimen of blood taken for culture on July 11, 1938, but cultures of four specimens taken since bacteriophage therapy was begun have remained sterile. The continued high temperature with hyperpyrexia at night would seem to be related to lesions in the brain, probably several small abscesses or a single

larger one in a region influencing heat regulation. There seems to be reason to hope that this lesion may be gradually walled off and organized by continuation of the present program. The urinary bleeding seems to have some relation to the administration of neoarsphenamine, and the use of this drug is being discontinued for the present."

On August 8 it was decided to discontinue the bacteriophage treatment, and on August 10 the patient was obviously much worse. At midnight her temperature reached 110 F. and blood again appeared in the urine. On the next morning there was rather severe renal colic. Bacteriophage treatment was renewed at 10 a. m. and continued daily. Blood was given intravenously, 360 cc. on August 11, 270 cc. on August 12 and 40 cc. on August 13.

The daily routine at this time included irrigation of the finger stump with 10 cc. of phage, the intravenous injection of phage morning and afternoon and the intravenous administration of 2 liters of 10 per cent dextrose in saline solution, later changed to 5 per cent dextrose in saline solution (September 10). The patient vomited part of every feeding, but her nutrition was remarkably well maintained. There was no emaciation. She was delirious and sometimes violent at night but nearly always rational during the day. Severe headache was persistent, and an ice cap was used continuously. On August 13 menstruation was evident, and on August 14 there were numerous swollen red wheals on the face. On August 15 and thereafter the patient was taken out on the roof for about a half-hour almost daily, and from September 21 to October 7 she was given daily treatment with ultraviolet rays.

Roentgen examination of the abdomen on August 20 gave negative results, and similar examination of the finger stump on August 27 revealed continuing osteomyelitis. The ocular fundi were examined by two consultant ophthalmologists on July 22, September 6, September 12 and September 22, without any positive findings. Roentgen examination of the head on September 14 revealed a slight accentuation of the lateral or sigmoid sinus on the left side, beginning back of the mastoid and extending almost to the median line. Some of us, who were familiar with the clinical behavior of the patient, were inclined to think that the obscure outline of the torcular Herophili, of the posterior portion of the superior longitudinal sinus, of the occipital sinus and of the mesial portion of the right lateral sinus might point to swelling of the brain substance and possible abscess of the brain located near the torcular Herophili and somewhat to the right of the median line. The evidence was not, however, accepted as convincing.

After fractional transfusions on September 14, 15 and 16 the patient seemed to be improved, and on September 17, with the use of cyclopropane anesthesia, the proximal phalanx of the left index finger was disarticulated at the base. This operation had been postponed for several weeks because of the critical state of the patient, and when it was finally done the reaction was unfortunate. The complaints of pain seemed in part hysterical. Frequent doses of codeine and of morphine were given on September 17, 18 and 19. On September 19 the morphine was discontinued. Most alarming was the development of severe pain over the left kidney associated with spasm of the left abdominal wall, even while the patient was receiving the sedatives. Atropine was given for several days. On September 24 there were a chill and a rise in temperature to 109 F. The perirenal pain extended to the right side. A culture of urine taken on September 26 yielded abundant colonies of the colon bacillus (approximately 2,000,000,000 organisms per cubic centimeter) but none of staphylococci. This colon bacillus was not fully susceptible to the stock colon bacillus phage which was in use; a specific bacteriophage, therefore, was prepared, and its injection was begun on Oct. 3, 1938.

Administration of calcium mandelate in doses of 3.5 Gm. four times a day was started on September 28, but the patient refused to take this on September 29, and it was discontinued. Her condition became less satisfactory, and there were severe chills at frequent intervals from September 30 to October 5, with marked abdominal distention on October 1 and 2. On October 3 the specific colon bacillus phage was given intravenously in place of the stock phage previously used, and on October 4 potassium citrate was given to render the urine neutral. As soon as this was accomplished the patient felt better. Unfortunately the citrate was discontinued for two days, and the severe renal pain returned at 4: 30 a. m. on October 8. The

Fig. 2.—Roentgenogram of the back of the head, taken on September 14. The interpretation was problematic, and the roentgenogram was considered normal.

patient went into alarming collapse at 10: 30 a. m. and was resuscitated by artificial respiration. She died early the following morning, October 9.

The jaundice which had been present in June, with an icterus index of 18.8 on June 6, had entirely disappeared, so that the icterus index on October 7 was 4.7 (normal).

Blood counts during the course of the illness had shown a remarkable lack of leukocytosis, but there was some leukocytic response to the acute infection of the urinary tract at the end of September. The severity of this infection was also evidenced by the rapidly developing anemia, as was shown by examination of the blood on October 4.

The remarkable feature was the long-continued high temperature. The possibility of fraud was given some consideration. We were inclined to exclude this, because the highest temperatures were observed by several persons present at the time and were associated with delirium. Trickery by the patient would be difficult to explain, because her left hand was covered with surgical dressings and an infusion of dextrose was running into a vein of the right forearm on many occasions while the rectal temperature was being taken. Friction by contraction of the anal sphincter was checked by simultaneous observation of rectal and oral temperatures, which checked reasonably well (on one occasion the rectal temperature was 104 F. and the oral temperature 103.4 F.; on another occasion the former was 105.2 F. and the latter 104.6 F.). Unfortunately, the temperature of the freshly voided urine was not tested, an oversight which we regret. Hysteria may present difficult puzzles. However, the neurologic consultants found no evidence of genuine hysteria, and such manifestations as prolonged anuria and hematuria and eventual death are not easily ascribed to hysteria, particularly in a patient confined

Examinations of the Blood

Date	Hemoglobin		Red Cells	White Cells	Percentage	
	Grams	Percentage			Polymorphonuclears	Lymphocytes
July 6	10.8	65	3,210,000	3,650	69	29
July 8	11.4	68	3,580,000	3,500	59	35
July 12 (a. m.)	....	..	.....	4,775	56	39
July 12 (4:35 p. m.)	....	..	.....	3,775	56	39
July 13 (9:10 a. m.)	....	..	.....	2,825	39	56
July 15	13.2	79	4,210,000	4,650	55	43
July 18	12.2	73	4,420,000	6,200	52	46
July 22	15.6	94	4,720,000	3,875	50	43
July 28	14.0	84	4,260,000	4,400	65	32
Aug. 8	11.0	66	3,600,000	6,200	73	24
Aug. 18	10.5	63	3,640,000	4,600	40	50
Aug. 31	13.0	78	3,910,000	5,200	38	56
Sept. 9	11.7	70	3,840,000	5,000	42	54
Sept. 26	11.4	68	3,630,000	8,850	65	29
Oct. 4	9.0	54	3,360,000	3,200	57	40

to bed and deprived of the use of her hands. It should be mentioned that the intravenous dextrose solution was given slowly because the patient vomited when it was given at the usual rate. Ordinarily the infusion was started about 2 p. m. and completed at midnight or shortly thereafter, and during this time any extensive movement was precluded. The patient cooperated well in this matter. Reinsertion of the infusion needle was not a simple and easy technical procedure in this case.

Necropsy was unfortunately delayed for twenty-six hours because death occurred early on Sunday and there was delay in obtaining permission from a relative far away. The well developed body showed no evidence of loss of weight. The finger tips were cyanotic, and there was a healing wound at the site of amputation of the left index finger. Edema of the extremities was absent.

There were marked cerebral edema and small areas of pial hemorrhage in the left frontal and parietal areas. On section there was marked congestion, particularly in the right basal ganglions and in the pons. In the left cerebellar medulla an irregularly outlined cavity occupied the major portion of the site of the dentate nucleus, the outer margin of which was distinctly recognized. The cavity extended to the right to involve the medial portion of the right dentate nucleus. Microscopically, disintegrating brain substance without evidence of reaction lined the cavity. Bacterial rods were seen in many sections, especially in those of the cerebellum.

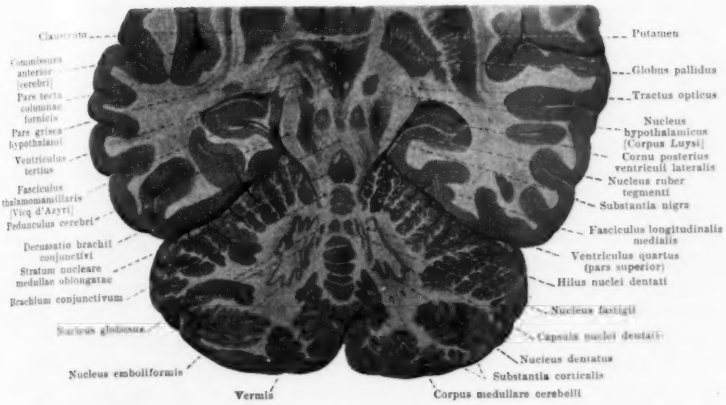

Fig. 3.—Section of the normal human brain, showing the nucleus dentatus, nucleus emboliformis and nucleus globosus and their relations (Spalteholz, W.: Hand-Atlas of Human Anatomy, ed. 2, translated by L. F. Barker, Philadelphia, J. B. Lippincott Company, 1906, vol. 3, p. 666, fig. 744).

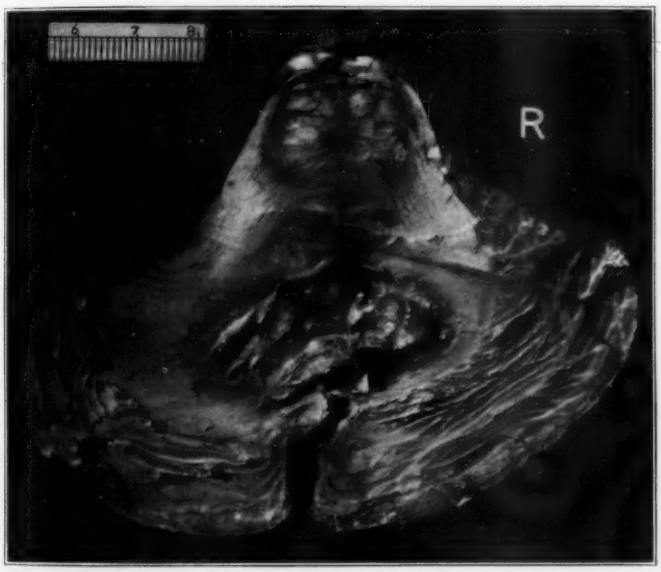

Fig. 4.—Section through the cerebellum of S. V., showing an irregular cavity involving the posterior part of the right dentate nucleus, the mesial portion of the left dentate nucleus and the posterior portion of the intervening vermis.

Pulmonary edema was present. Myocardial degeneration, fibrosis and hypertrophy were seen in moderate degree, as well as coronary arteriosclerosis and aortic atherosclerosis. In the pancreas there were diffuse fibrosis and prominent hyalinization of the islets of Langerhans. In the kidneys there was acute pyelonephritis, most marked in the renal substance. The pelvic area presented evidence of an older process, with scarring, thickening and focal collections of lymphocytes and fewer plasma cells. There was also chronic cystitis.

The irregular cavity in the cerebellum excited great interest, but its nature was not established. The possibility that there may have been a relatively benign glioma of the type of astrocytoma fibrillare, with cystic degeneration, was considered. Such a tumor may exist for years and may sometimes be associated with vague nervous manifestations and complaints leading to abdominal and pelvic operations. Special studies of the cerebellar tissue about this cavity failed to reveal any convincing evidence of such a neoplasm.

COMMENT

Hyperthermia is sufficiently rare to constitute a challenge to careful and precise observation. This patient was studied with unusual care, and no effort was spared to bring about her recovery. However, those caring for her had other duties, and there was not much spare time for nonessentials.

In study of the record, one may conclude that the high temperatures recorded were fabrications due to trickery of the patient or to carelessness of the observers, that the patient was a chronic malingerer, that the irregular cavity in the cerebellum was entirely due to postmortem disintegration and that the edema of the cerebral cortex and the hemorrhages in the basil ganglions were entirely agonal. Such a conclusion would lead one to discard the case altogether. As one physician put it: "Such temperatures would occur only in a nurse."

Most physicians, however, are inclined to accept bedside records as reasonably reliable. Perhaps we may be too gullible, but we do not think so. Those who were in personal contact with this patient during life found no reason to suspect trickery. There was some consistency in the observations. One may assume that the amputation on June 21 had dislodged some staphylococci and permitted their transportation to the cerebellum, where a destructive lesion slowly developed. Her fall on June 28 while walking and her unsteadiness on July 1 were suggestive of a cerebellar lesion. The itching was evidently associated with icterus, and this in turn was related to the sepsis. The invasion of the blood stream by Staphylococcus aureus was convincingly proved by cultures of blood taken by two different persons on July 8 and 11 and seeded in each instance into two flasks of broth and three agar plates. The remarkable rise in temperature on July 12 resembled closely the response to bacteriophage therapy in sepsis, but in this instance it was excessive. At this time the body was hot and the patient was irrational. The subsequent temperature record was highly atypical considering

that blood culture was negative after bacteriophage sterilization of the blood stream, and it suggested a localization in the brain. Roentgen studies on September 14 revealed irregularities in the dural sinuses suggesting, but not proving, alteration of pressure relations in the cerebellum. At necropsy the brain revealed evidence of disturbed pressure relations, with edema of the cerebral cortex, congestion and extravasations of blood in the basal ganglions and an irregular ragged cavity in the cerebellum. Postmortem changes obscured the picture, and the nature of this cavity remains uncertain. It is, however, possible that it may have marked the site of a stapylococcic abscess which had become sterilized and quiescent, only to be again invaded by the colon bacilli in the terminal days of the illness. The terminal phenomena, particularly the respiratory collapse on October 8, might well have resulted from compression of the medulla, forcing it downward into the foramen magnum.

If this view of the record is accepted, this case would seem to shed some light on the problem of hyperthermia. It is a matter of sincere regret that the clinical observations have not been critically exact and that the necropsy study leaves something to be desired. Nevertheless, cases of hyperthermia are so rare and the subject is so important and still so obscure that a detailed record seems justified.

SUMMARY AND CONCLUSIONS

Hyperthermia remains a controversial problem.

Temperatures in man above 46 C. (114.8 F.) should not be accepted as genuine without most critical examination of the evidence. There are sound theoretic and experimental reasons for this attitude.

Temperatures in man between 42 C. (107.6 F.) and 46 C. (114.8 F.) should be subjected to skeptical and critical scrutiny. Such observations should be supported by testing with multiple thermometers held by reliable observers simultaneously in the axilla, the mouth and the rectum and by observations of the temperature of the freshly voided urine and feces. While many reported observations in this range are undoubtedly genuine, there are also some reports in this category which are highly questionable.

Records are presented of a patient who had prolonged hyperthermia. She eventually died and necropsy was performed. Unfortunately the observations were not adequately checked according to the methods just described, but they are believed to be valid.

At necropsy there was found an irregular cavity of problematic nature in the cerebellum near the left dentate nucleus.

MULTIPLE MYELOMA

ASSOCIATED WITH NODULAR DEPOSITS OF AMYLOID IN THE MUSCLES AND JOINTS AND WITH BENCE JONES PROTEINURIA

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The occurrence of typical and atypical amyloidosis associated with multiple myeloma is now well recognized.[1] Atkinson[2] in a review of 643 recorded cases of multiple myeloma found amyloid reported in 40, or an incidence of about 7 per cent. Unusual amyloid tumor formation and localization are cited by Helly,[3] Randall,[4] Glaus[5] and Askanazy.[6] The cases of multiple myeloma in which amyloidosis is atypical in its distribution or type are considered in this paper. In them, besides the underlying myeloma, there are amyloid masses in varying number and size distributed throughout the body. In certain cases the amyloid is found particularly in the voluntary musculature and in the joints, so that the clinical picture closely resembles that of rheumatoid arthritis. A survey of the literature reveals that there have been only 11 recorded cases of this type. It will be noted from the table that those first reported in the American literature were described by Michelson and Lynch[7] in 1934 and

From the Departments of Medicine and Pathology of the New York Hospital and Cornell University Medical College.

1. Magnus-Levy, A.: (*a*) Bence-Jones Eiweiss und Amyloid, Ztschr. f. klin. Med. **116**:510, 1931; (*b*) Multiple Myelome: VII. Euglobulinämie; Zur Klinik und Pathologie; Amyloidosis, ibid. **126**:62, 1933.

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6. Askanazy, M.: Ueber knötchenförmige lokale Amyloidbildung in der Darmmuskulatur, Verhandl. d. deutsch. path. Gesellsch. **7**:32, 1904.

7. Michelson, H. E., and Lynch, F. W.: Systematized Amyloidosis of Skin and Muscles, Arch. Dermat. & Syph. **29**:805 (June) 1934.

Rosenblum and Kirshbaum [8] in 1936. In neither of the cases was an autopsy performed. We herewith report a case with complete clinical and postmortem study.

Tumor-like masses of amyloid in association with multiple myeloma have been described by Hueter and others, as shown in the accompanying table. In cases in which an autopsy was performed, the anatomic observations were very similar to ours. Hueter [9] aptly described the amyloid material in the tumor masses as resembling fish flesh. The amyloid in the joints resembled closely that seen in our case, both grossly and microscopically. It is noteworthy that in the cases collected from the literature, as well as in ours, there was scant deposition of amyloid in the liver, spleen and kidneys. This lack of involvement of the usual sites is characteristic of most atypical amyloidosis. It is particularly characteristic of the condition designated as primary amyloidosis,[10] accompanying which there is no recognized disease.

REPORT OF A CASE

A white woman 45 years old was first seen in the medical clinic of the New York Hospital on March 4, 1935. She complained of having had (1) an ache in the lower part of the back for years, (2) pain in the back of the neck and shoulders during the past years and (3) spells of weakness and fever during the past two weeks.

Her past medical history revealed typhoid fever at the age of 20, diphtheria at 24 and attacks of influenza at 24 and 28.

Her family history was irrelevant.

Examination.—Her temperature was 98.6 F., and her pulse rate, 80 per minute and regular. Her blood pressure was 130 systolic and 80 diastolic. Careful physical examination by different observers disclosed nothing significant.

Laboratory investigation revealed a negative Wassermann reaction of the blood, a red blood cell count of 4,000,000, with 72 per cent hemoglobin (Dare method), and 12,000 white blood cells, with a normal differential count. The urine on the first examination gave a 4 plus reaction for albumin but showed no sugar. Microscopically, clumps of white blood cells were observed. On two other occasions the routine laboratory examinations showed a 1 or 2 plus reaction for albumin, with a varying number of polymorphonuclear leukocytes. The basal metabolic rate was —12 per cent.

In view of the findings a tentative diagnosis of pyelitis was made. On cystoscopic examination intravenously administered dye appeared within two to three

8. Rosenblum, A. H., and Kirshbaum, J. D.: Multiple Myelomas with Tumor-Like Amyloidosis: Clinical and Pathologic Study, J. A. M. A. **106**:988 (March 21) 1936.

9. Hueter, C.: Ungewöhnliche Lokalisation der Amyloidsubstanz in einem Falle von multiplem Myelom (Amyloid des Darms, der Thoraxmuskulatur, des Schultergelenks), Beitr. z. path. Anat. u. z. allg. Path. **49**:100, 1910.

10. Lubarsch, O.: Zur Kenntnis ungewöhnlicher Amyloidablagerungen, Virchows Arch. f. path. Anat. **271**:867, 1929.

Summary of Cases of Amyloid in Association with Multiple Myeloma

Case	Age and Sex	Author	Striated Muscles	Joints	Joint Spaces	Bence Jones Protein	Kidney	Comment
1	58 M	Hueter [9]	Large masses in deltoid, serratus magnus	Left shoulder; others not examined	Numerous free masses of amyloid	+	Contracted; condition regarded as nephritis	Myeloma, regarded as cause of amyloid
2	39 M	Zeehuisen [11]	Countless masses of varying size	Numerous joints	Not mentioned	42 Gm. daily for three weeks	Not mentioned	Cited by Magnus-Levy
3	46 M	Buch [12]	Numerous large masses	Shoulders and hips	Filled with amyloid	?	Not mentioned	Cited by Magnus-Levy
4	?	Wiessner [13]	Diffuse muscular involvement	Hips, knee joints	Filled with amyloid	?	Not mentioned	No clinical data
5	46 F	Magnus-Levy [1]	In inguinal region	Shoulders, hands, knees, sternoclavicular joints	Numerous masses	++	Chronic "nephrosis"	Diagnosed in life; proved by autopsy
6	56 M	Magnus-Levy	None visible	Shoulders, elbows, fingers stiff	Not examined	+	Not mentioned	No autopsy
7	57 M	Paul [14]	Jaw muscles, tongue, pharynx, masses	Shoulder	Not examined	+	Not mentioned	Extensive amyloidosis
8	38 F	Paige [15]	Large masses in both deltoids	Shoulders and sternoclavicular joints	Glenoid fossa (small amounts)	+	Involved by amyloid	Extensive amyloidosis in all organs except liver
9	54 M	Michelson, Lynch [7]	Macroglossia, cutaneous amyloid	Hips, hands	Not examined	+	Clinically diminished function	Roentgenograms similar to those of case 12; no autopsy
10	39 F	Rosenblum, Kirshbaum [8]	Chest muscles, masses	Pain in hips and spine; stiffness of joints	Not examined	+	Patient died in uremia	Clinical diagnosis, biopsy and roentgenograms; no autopsy
11	38 M	Stewart [10]	Large masses over body	Numerous joints	Not examined	+	Not mentioned	Clinical report; no autopsy
12	45 F	Tarr and Ferris	Numerous masses in muscle attached to bone	Numerous	Filled with amyloid	+	Nephrosclerosis	

11. Zeehuisen, H.: A Case of Albumosurie, Nederl. tijdschr. v. geneesk. **29**: 829, 1893; cited by Magnus-Levy.[1a]
12. Buch, H.: Ein Fall von multipler primärer Sarcomatose des Knochenmarkes, und eine eigenthümliche Affection der vier grossen Gelenke, Dissert., Halle, Lipke, 1873; cited by Magnus-Levy.[1a]
13. Wiessner, R., cited in Zentralbl. f. allg. Path. u. path. Anat. **50**: 127, 1931.
14. Paul, F., cited in Zentralbl. f. allg. Path. u. path. Anat. **50**: 127, 1931.
15. Paige, B. H.: A Case of Myeloma with Unusual Amyloid Deposition, Am. J. Path. **7**: 691, 1931.

minutes from each ureteral orifice. Retrograde pyelograms showed normal renal pelves. Catheterized urine contained only a few isolated white blood cells. It was not tested for albumin.

At this time fluctuation of the amount of albumin in the urine (reactions ranging from 1 plus to 4 plus), apparently unrelated to the number of white blood cells present, suggested the possibility of Bence Jones proteinuria. The urine was tested with this in mind on May 10 and found to yield a cloudy precipitate at 55 C. This increased in intensity as the heating continued and then diminished slightly on boiling. Filtering the boiling urine yielded a clear solution which showed a cloudy precipitate on cooling to about 60 C. Dilute acetic acid intensified the reaction. Subsequent specimens of urine all behaved in the same fashion.

Roentgen examination of the skull, spine, long bones and chest revealed no significant changes. A blood film on June 3, reviewed by the hematology department, showed 7 per cent young polymorphonuclears, 34 per cent adult polymorphonuclears, 52 per cent lymphocytes, 4 per cent large mononuclears, 2 per cent eosinophils and 1 per cent basophils. The red blood cells showed slight anisocytosis with moderate central pallor. The white blood cells were not obviously increased in number. The percentage of lymphocytes was somewhat increased, with a rare immature lymphocyte. No abnormal white blood cells were seen.

Chemical studies made of the blood on June 4 revealed the following values per hundred cubic centimeters: serum calcium 9.5 mg., total proteins 7.0 Gm., serum albumin 3.3 Gm., serum globulin 2.5 Gm. and urea nitrogen 14.0 mg.

Course.—Because of all these inconclusive findings, a bone marrow puncture and an intravenous congo red test for amyloidosis were contemplated, but the patient refused to cooperate in any further tests and failed to return to the clinic after June 1935. However, we later learned that there was a steady progression of her symptoms. The pain in the back spread, so that it involved the hips and inner surfaces of the thighs. She also had progressive stiffness of the shoulders, elbows and knees with pain on motion in all these joints. The condition was regarded as arthritis by most of the physicians who treated her in the two and a half years prior to her second admission to the hospital. In June 1937 she was forced to give up her clerical work. For the two months prior to the second admission there were edema of the ankles and puffiness of the face.

On admission to the New York Hospital on Jan. 9, 1938, she was thin, emaciated and acutely ill, with obvious distress on even slight movements. Numerous small shotty nodes were present in the axillas and in the posterior cervical region. The anterior cervical nodes were larger and less firm. No inguinal nodes were palpable. In addition, firm masses of variable size and not tender were seen and felt in different parts of the body (fig. 1). Their symmetric distribution is worthy of note. There was a mass about 3 by 3 cm. just in front of each ear and overlying the mandibular joint. There were smaller, less firm nodules in each antecubital fossa. In each axilla anterior to the lateral border of the scapula were similar, but larger, firm round masses apparently attached to the scapulas. The skin was freely movable over these masses.

The shoulder and elbow joints were stiff but permitted slight motion. The right index finger was semiflexed and stiff. There was limited motion of the hips. The knee joints were enlarged but not fluctuant. The right ulna was rough, and over the middle of this bone was a small firm subcutaneous nodule. Little gross deformity of any joint and only slight tenderness on pressure were noted. Three plus pitting edema extended from the feet to the upper third of the calves. The head was normal in size and shape with no tenderness or defect of the calvarium.

The eyes and the fundi were not remarkable. The heart was found not enlarged on percussion and palpation, and its rate was regular. The blood pressure was 124 systolic and 64 diastolic. The lungs were clear. The abdomen was flat, with the edge of the liver firm and palpable 3 fingerbreadths below the costal border in the midclavicular line. There was tenderness on deep palpation in the left flank. The results of pelvic and rectal examinations were not remarkable. Reflexes were normal.

The disease ran a febrile course. The irregular temperature went to 103 F. and the pulse rate to 140. Despite two blood transfusions the patient's progress was steadily downgrade, with death four weeks after admission to the hospital.

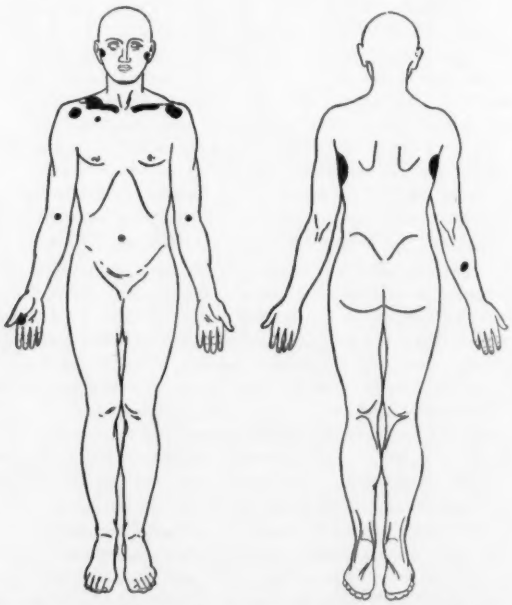

Fig. 1.—The distribution and relative size of the amyloid tumors, shown in solid black.

Laboratory Studies.—A small nodule near the left scapula and one over the right ulna were removed under local anesthesia. The mass near the scapula was found between the muscles. It was yellowish, was of homogeneous structure and when cut showed the consistency of firm gelatin. The nodule over the ulna did not shell out easily and seemed fixed to the underlying structures. Microscopically the pieces appeared similar and were seen to consist of plugs of light-staining hyaline relatively acellular tissue, with a tendency to form whorls. A few small blood vessels were scattered throughout.

Large amounts of Bence Jones protein were present constantly in the urine, and in addition there was a 1 plus reaction for albumin. There were always 20 to 30 white blood cells per high power field, with a few granular casts. The specific gravity ranged from 1.007 to 1.027. A typical blood study showed 2,100,000

red blood cells, with 45 per cent hemoglobin, and 6,000 white blood cells, with 28 per cent adult polymorphonuclears, 30 per cent lymphocytes, 4 per cent monocytes and 4 per cent basophils. Two nucleated red blood cells per hundred white blood cells and occasional plasma cells were seen in the smear (Dr. C. E. Forkner). The erythrocytes showed poikilocytosis, anisocytosis, microcytosis, polychromatophilia, stippling and Cabot rings. The blood coagulation time was ten minutes and the bleeding time two minutes. The clot retraction was excellent and fragility normal. Chemical studies of the blood gave the following results:

	Jan. 10	Jan. 19	Jan. 24	Feb. 2
Urea nitrogen, mg. per 100 cc.....	10		26	
Serum phosphorus, mg. per 100 cc.....	3.6			
Serum phosphatase, units.....	5			
Serum calcium, mg. per 100 cc.....	9			
Serum albumin, Gm. per 100 cc.....	3.1	2.6		2.5
Serum globulin, Gm. per 100 cc.....	0.6	1.1		0.4
Plasma chloride, mg. per 100 cc.....	560			
Carbon dioxide, volumes per cent.....			46	
Icteric index				5

There was no evidence of Bence Jones protein in the serum filtered at the boiling point and then cooled. A congo red test showed that 72 per cent of the dye was removed from the blood stream in one hour. The normal rate is about 30 per cent in one hour. Renal function tests with phenolsulfonphthalein showed 51 per cent excretion in one hour shortly after admission and 23 per cent one week before death.

Roentgenologic examination on January 10 of the skull, chest and long bones revealed a mottled, somewhat discrete, minute, rounded osteolytic process throughout the proximal ends of the humeri and the femors, with a suggestion of a similar process in the left frontal region of the skull. Changes in the ribs were not definite. There was evidence of localized demineralization in both femurs, wrists and hands.

Diagnosis.—Multiple myeloma had been suspected when the patient was first seen in 1935. The nature of the tumor masses was uncertain, but it was thought that they were part of the underlying disease. In view of the long-standing Bence Jones proteinuria it was believed that there was a definite renal lesion. The peripheral edema was attributed to the severe hypoproteinemia.

Postmortem Examination.—An autopsy was performed twenty-four hours after death. General inspection revealed changes essentially the same as those described clinically. Approximately 450 cc. of clear yellow fluid was in each pleural cavity.

The heart weighed 280 Gm. There were small deposits of fat beneath the endocardium of the left ventricle.

The lungs weighed 1,500 Gm. They were deep red, and the lower parts were much less crepitant than usual.

The spleen weighed 310 Gm. and was not remarkable.

The stomach, intestines and pancreas were without noteworthy change.

The liver weighed 1,680 Gm. On the cut surface the lobular architecture was distinct, with mottled, pale, translucent grayish and light yellow areas.

The adrenals were not remarkable.

The kidneys weighed 135 and 130 Gm. and were firm and pale reddish pink. The capsules stripped readily, despite the presence of numerous, diffusely distributed small depressed areas in the cortex from 0.3 to 0.7 cm. across. On the cut surface

the usual cortical architecture was not distinct, and the medulla and the cortex were poorly differentiated. In some places the cortex measured only 0.3 cm. in thickness. The pyramids were somewhat more translucent and paler than usual.

Aside from a few small scattered hemorrhages in the bladder mucosa there were no changes in the pelvic organs.

The pharynx, larynx, esophagus and thyroid were not remarkable. Two parathyroid glands were found on each side, the right lower one being somewhat larger than the others, and all were uniform in consistency and shape. After fixation in formaldehyde they weighed together 139 mg.

The cut surface of the vertebrae was mottled grayish white and light red. In a few places the soft, lighter tissue formed somewhat indistinctly demarcated nodules, the largest not over 0.6 cm. across. The marrow of the sternum and

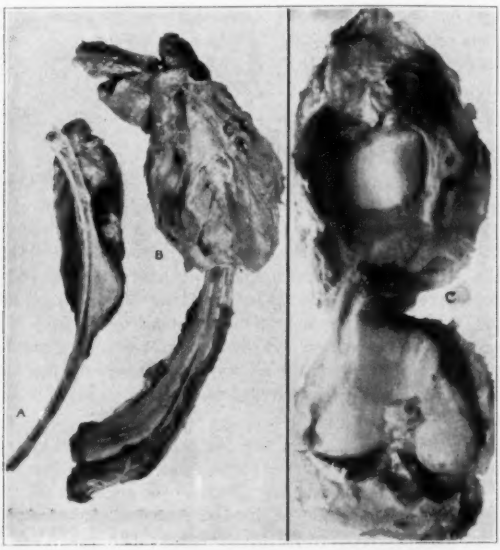

Fig. 2.—*A* and *B*, ribs with attached amyloid masses. *A*, Several rounded nodules of myeloma in the longitudinally split rib. *B*, the laminated structure of an amyloid tumor. *C*, the right knee joint, opened, with the patella reflected upward. Villous deposits of amyloid attached to the synovial membrane are most conspicuous at the margins of the patella and near the upper edge of the articular surface of the tibia. Much more similar material was loose in the knee joint.

ribs was of similar appearance (fig. 2 *A*). The marrow trabeculae of all these bones were softer than usual, obviously owing to partial decalcification. The bones of the skull were hard, and no nodules of tumor or areas of rarefaction were found.

Both knee joints and the right acromioclavicular joint were opened. In the cavity of each knee joint was an increased amount of sticky, reddish fluid. Somewhat gelatinous, translucent pink material formed villous projections from the

synovial membrane and was found free in the joint cavities (fig. 2 *C*). The articular surfaces were not eroded, nor were there deposits on the cartilage. The acromioclavicular joint was similar in appearance.

Attached to the periosteum of the lateral aspect of the right fifth and sixth ribs was a firm mass that measured approximately 11 by 6 by 2.5 cm. On section it was found to consist of layers of generally homogeneous, yellowish pink translucent material suggesting cartilage. Some of this substance was easily dislodged in small solid sheets (fig. 2 *B*). A few centimeters posteriorly, attached to the fifth rib, was a smaller mass of similar material, about 2.5 cm. across. Adherent to the left fifth rib was a mass which measured 10 by 5 by 2 cm. It was somewhat firmer than those on the right. It contained scattered small yellow foci. All of these masses were loosely attached to the ribs so that they could be moved and were not continuous with the bone itself. They appeared to push aside the adjacent muscles rather than to invade them. Firm, translucent hyaline tissue was intimately attached to the left clavicle near its medial and lateral ends, forming nodular elevations of the surface. About the head of the right humerus was a large mass of hyaline material that fused with the periarticular tissue.

The lymph nodes near the head of the pancreas were enlarged, firm and somewhat flattened. The para-aortic nodes were slightly enlarged and reddish.

The pituitary body was not unusual. The brain and meninges, aside from slight thickening of the arachnoid in the interpeduncular space, were not remarkable.

Microscopic Examination.—In one medium-sized artery of the heart the media was extensively replaced by pink-staining homogeneous material resembling amyloid.

In the media of a few small blood vessels there was a scant amount of hyaline material. In the lumens of the alveoli were many red blood cells and numerous large mononuclear phagocytes containing brown pigment granules. Slight bronchopneumonia was evident. In one of the larger vessels was a mass of leukocytes, among which were a number of cells resembling plasmacytes.

In the spleen the connective tissue was slightly increased. In the congested pulp were seen many large mononuclear cells, of which some were apparently myelocytes, while others resembled plasma cells.

There was some increase in interacinar and interlobular connective tissue in the pancreas.

Fatty vacuolization of the liver cells without zonal distribution was present. In the connective tissue of the portal spaces were scattered lymphocytes and larger mononuclear cells, with a few plasma cells.

There were focal scars on the cortex of the kidney, increased connective tissue, atrophy of some tubules and dilatation of others. In the cytoplasm of some of the convoluted tubules were small hyaline droplets of varying size. Sudan IV stain showed a few fatty droplets. The tufts of most of the glomeruli in the scars were partially or completely replaced by bright eosinophilic material. Many glomeruli in other areas contained smaller amounts. In the lumens of the convoluted tubules there was a granular pink albuminous precipitate, while in many of the straight collecting tubules there were masses of more intensely bright eosinophilic granules, or homogeneous casts, formed apparently by fusion of the granules (fig. 3 *D*). The lining epithelium of many tubules was flattened and in places was difficult to recognize. Adjacent to the casts were frequently seen large mononuclear cells and large multinucleated cells of the foreign body type. In places these giant cells partially surrounded the hyaline material or were in intimate contact with it. A pink-staining homogeneous substance resembling

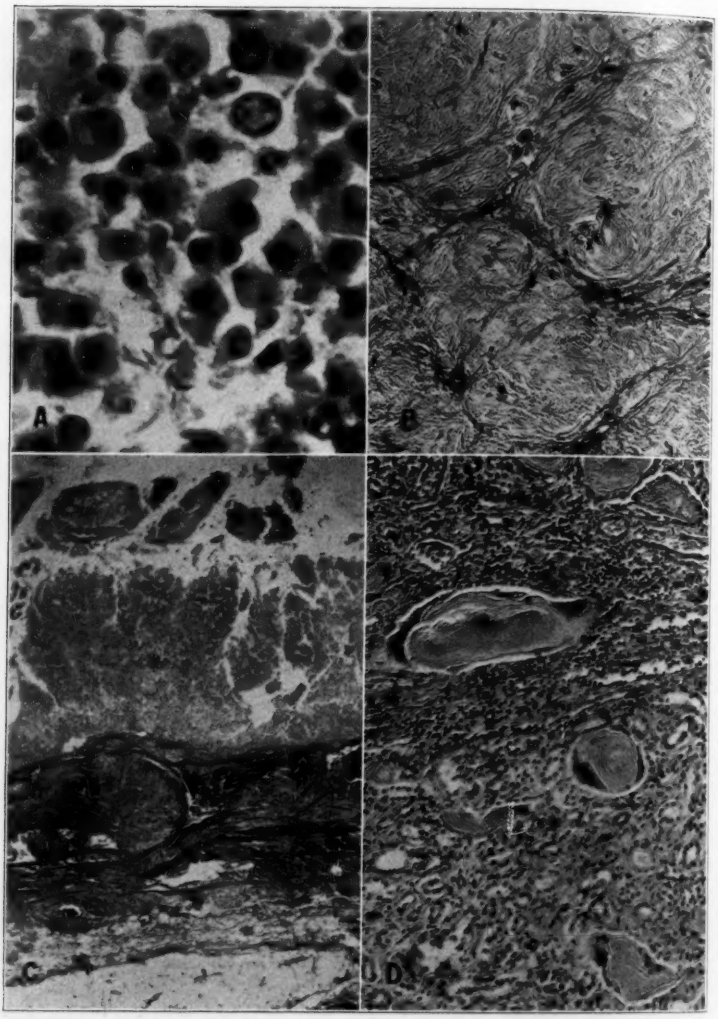

Fig. 3.—*A*, cells resembling plasma cells in the marrow of the sternum (hematoxylin and eosin, × 771). *B*, nodules of amyloid in one of the masses attached to the ribs, showing delicate trabeculae of connective tissue (Van Gieson's stain, × 95). *C*, distribution of amyloid deposit on synovial membrane of the knee joint, showing lack of involvement of the underlying connective tissue (× 25). *D*, hyaline, partly lamellated casts in the tubules of the kidney. Multinucleated giant cells are seen in the edges of the material. There is an infiltration of lymphocytes in the adjacent tissue (× 95).

amyloid was in the media of a few moderate-sized arteries. The capillaries of the medulla contained large mononuclear cells closely resembling plasmacytes.

Practically the whole lymph node of the pancreas was replaced by diffusely distributed large mononuclear cells resembling plasmacytes. Radial arrangement of the chromatin and perinuclear clear zones in the cytoplasm were rarely seen.

In the parathyroids clear cells were not numerous. Several small vessels with thickening of their walls contained deposits of pink hyaline material in their media.

The marrow of the vertebrae and sternum was almost entirely replaced by closely packed cells resembling those found in the pancreatic lymph node (fig. 3*A*). In the femur and ribs were foci of hematopoietic tissue containing cells of the myeloid and erythrocytic series.

The masses attached to the bones were composed of homogeneous or fibrillar material which varied in its staining with eosin from deep to light pink. In it were scattered connective tissue cells. The substance was subdivided into nodules or lobules of varying size by strands of deeper pink (fig. 3*B*). Thin-walled blood vessels were numerous and usually surrounded by delicate strands of connective tissue in which were a few plasma cells and lymphocytes. In a section removed from a nodule attached to the left clavicle were several multinucleated giant cells embedded in the homogeneous material. In the periarticular mass of the right shoulder, pink homogeneous material blended with the cartilage. The pink-staining material described previously was very suggestive of amyloid.

In the knee joints and in the right acromioclavicular joints, masses of pink-staining granular, fibrillar or homogeneous material were attached to, and intimately fused with, the synovial membrane (fig. 3*C*). Into this substance extended delicate strands of connective tissue with a few cells and thin-walled blood vessels. The surface was irregular, and mesothelial cells of the synovial membrane were recognized in only a few areas.

Frozen sections of the kidney and of the masses attached to the ribs, fixed in 4 per cent formaldehyde, were stained with iodine and sulfuric acid, cresylecht violet, gentian violet and acetic acid, and iodine green.

With iodine and sulfuric acid, light brown deposits were seen in many glomeruli of the kidney. The dense casts in the straight and collecting tubules were also brown, the outer layers being usually darker and occasionally greenish blue. The homogeneous material in an extracostal mass was stained greenish blue in contrast to the yellow of the connective tissue, and here similar greenish material was in the walls of several small arteries. These staining reactions suggest amyloid.

With cresylecht violet and with gentian violet and acetic acid, typical metachromatic staining for amyloid was obtained in the kidney. In the costal mass the pink staining of the homogeneous nodules was in sharp contrast with the inconspicuous staining of the connective tissue. Preparations with iodine green failed to give metachromatic staining. Differential stains for connective tissue, after fixation in Zenker solution (prepared with formaldehyde) and embedding in paraffin, were also employed. With Mallory's aniline blue stain the hyaline deposit, wherever found, i. e. in the glomeruli of the kidneys, the walls of the arteries, knee or shoulder joints or masses attached to the bones, took a somewhat lighter blue stain than the collagenous connective tissue. The more granular casts in the renal tubules were bright crimson, and this color was found in the centers of hyaline casts whose outer layers were homogeneous deep blue.

Van Gieson's stain was combined with the Verhoeff stain for elastic tissue. The hyaline material in the connective tissue masses, in the joints and in the renal glomeruli was orange-yellow, in distinct contrast to the bright canary yellow of the epithelial cells and the muscle and the bright red of the collagenous tissue.

The casts in the tubules stained varying shades of yellow and yellowish brown. The droplets in the tubular epithelium were light brownish yellow, in contrast to the brighter yellow of the remaining cytoplasm.

COMMENT

From the clinical point of view this patient's course presented several unusual features. There is little doubt that the bone marrow was involved by the neoplasm when the patient was first examined, yet complete roentgenologic studies failed to reveal it. Even terminally the roentgenogram was not at all conclusive or characteristic of multiple myeloma. Similar roentgenologic findings are mentioned in several of the cases in the literature, notably those of Michelson and Lynch [7] and of Stewart.[16] The condition is easily mistaken for osteoporosis associated with inactivity or inanition.

Studies of the blood in the early stages were disappointing because they gave little information. There was no hyperproteinemia [17] or hypercalcemia. Toward the end of the patient's illness severe hypoproteinemia, with a serum globulin content of 0.4 per cent and a serum albumin content of 2.5 per cent was noted. Hypoproteinemia in the course of multiple myeloma has been described by Chester [18] and is attributed to the degree of undernutrition. The occurrence of an occasional plasma cell in the blood smear was the only significant observation in stained smears of the blood. Plasma cell leukemia has been reported by several authors, including Beck and McCleary,[19] Muller and McNaughton [20] and Piney and Riach.[21]

The only constant finding in favor of the diagnosis of myeloma was the Bence Jones proteinuria. In 10 of the 12 cases of multiple myeloma with amyloid tumors recorded in the literature, Bence Jones protein was found in the urine. It was not mentioned in the other two reports. The absence of this substance in the urine in the reported cases of atypical amyloidosis without myeloma is noteworthy.

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16. Stewart, A.: Myelomatosis, Quart. J. Med. **7**:211, 1938.

17. Perlzweig, W. A.; Delrue, G., and Geschickter, C.: Hyperproteinemia Associated with Multiple Myelomas: Report of an Unusual Case, J. A. M. A. **90**:755 (March 10) 1928. Bing, J.: Some Cases of Hyperproteinaemia, Acta med. Scandinav. **88**:478, 1936.

18. Chester, W.: Multiples Myelom und Hypoproteinämie, Ztschr. f. klin. Med. **124**:466, 1933.

19. Beck, H. G., and McCleary, S.: Multiple Myeloma with Bone Marrow Plasma Cells in the Blood, J. A. M. A. **72**:480 (Feb. 15) 1919.

20. Muller, G. L., and McNaughton, E.: Multiple Myeloma (Plasmacytomata) with Blood Picture of Plasma Cell Leukemia: Report of Two Cases, Folia haemat. **47**:17, 1932.

21. Piney, A., and Riach, J. S.: Multiple Myeloma, Aleukemic and Leukemic, Folia haemat. **47**:37, 1932.

The gradual development of "arthritis" in the course of multiple myeloma should arouse suspicion as to its origin. Clinically the resemblance to rheumatoid arthritis may be very close. (Excellent photographs illustrating the deformities of the joints are found in Stewart's [16] article). The pain and the disability in the joints are caused by the deposition of amyloid in the joint spaces and periarticular tissue. With the large joints it is at times difficult to decide whether these masses are in the surrounding muscles or are part of the joint. The occurrence of such masses in the voluntary muscles and along the bones offers a clue to the true nature of the pathologic condition in the joints. In our case, the time of the first appearance of the masses was not known, but, judging from their size, it is safe to assume that they were present for from several months to a year. A similar time interval is noted in the cases reported in the literature. The clinical identification of these masses as amyloid is at times difficult. The congo red test may be inconclusive or may even give negative results. In our case the results suggested the presence of amyloid.

From the pathologic standpoint several observations are of interest. The myeloid tumor of the bones was widespread, and, while in a few areas it was composed of somewhat circumscribed small nodules, in general it consisted of a diffuse replacement of the marrow. This is in contrast to the usual formation of distinct nodular masses of tumor in multiple myeloma. The absence of involvement of the skull was unusual. Microscopically the neoplasm was seen to be composed of cells which resembled plasma cells in several respects but were not typical, because in general the cytoplasm was not as homogeneous as that of typical plasma cells and did not contain a conspicuous perinuclear clear zone. However, these cells were similar to those usually found in what is commonly called a plasma cell myeloma. The presence of a few cells resembling plasma cells in capillaries of the kidney and in a blood vessel in the lung confirmed the clinical observation on the blood smear.

The deposition of hyaline frequently laminated material, presumably Bence Jones protein, in the tubules of the kidney and the scarring of that organ consequent on tubular obstruction have been well described by several authors, including Bell,[22] who has made an extensive review of the literature. Forbus and his associates [23] have also recorded a case. MacMahon and Magnus-Levy [24] have recently described the experi-

22. Bell, E. T.: Renal Lesions Associated with Multiple Myeloma, Am. J. Path. **9**:393, 1933.

23. Forbus, W. D.; Perlzweig, W. A.; Parfentjev, I. A., and Burwell, J. C.: Bence Jones Protein Excretion and Its Effect upon the Kidney, Bull. Johns Hopkins Hosp. **57**:47, 1935.

24. MacMahon, H. E., and Magnus-Levy, A.: Renal Lesions in Experimental Bence Jones Proteinuria, Am. J. Path. **12**:763, 1936.

mental production of renal lesions in rats by injection of Bence Jones protein. They found deposits in the tubules which took a golden orange with Mallory's aniline blue stain. They found similarly staining granules in the cytoplasm of the cells lining the tubules and assumed that they were related to the material in the lining of the tubules. Although it was not specific, they thought this stain of importance in identifying the substance. This belief was not confirmed, however, by Forbus.[25] It is noteworthy that in our case part of the tubular deposits took a deep crimson with Mallory's stain, a reaction not obtained with any of the other hyaline deposits in the case. The staining blue of the outer layers of many of the casts, a reaction shown by amyloid, is of interest in view of the relation of Bence Jones protein to amyloid, as suggested by Magnus-Levy.[1] He expressed the belief that in multiple myeloma the protein acts as the mother substance to the amyloid. He has demonstrated in stained specimens what appears to him a gradual transition of one to the other. Experimental evidence to confirm this suggestion was not found by MacMahon.[26] With the Van Gieson stain we found no consistent differential staining of the casts. With iodine and sulfuric acid and the metachromatic stains the casts which were not distinguishable from amyloid in their reactions, though they varied in intensity of staining. The occurrence of multinucleated giant cells in close relation to the tubular casts indicates the insoluble nature of the material and suggests that it was present for some time in the tubules. It conforms with the belief that the cortical scars are directly the result of obstruction and stasis. The presence in the renal glomeruli of homogeneous material which gave typical reactions to several of the tests for amyloid complicates the renal picture. Accompanying this is hyaline droplet degeneration of the cells of many of the convoluted tubules, a change often found with renal amyloidosis. None of the droplets stained a golden orange with Mallory's aniline blue, as described by MacMahon in his animals, but with Van Gieson's stain they took a color distinctly different from that of the remainder of the cytoplasm, and with aniline blue many were bluish.

Chemical studies of amyloid tumors[27] have revealed no constant composition of the material. It is probable that differences exist between the amyloid found in the liver, spleen and kidney in the usual widely distributed disease and that in the atypical localized deposits. These differences may explain the variations in staining reactions so often observed.

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25. Forbus, W. D., in discussion on MacMahon and Magnus-Levy.[24]

26. MacMahon, H. E., in discussion on Robertson, H. E., and Brunsting, L. A.: Amyloidosis with Unusual Distribution and Bence Jones Protein, Am. J. Path. **12**:767, 1936.

27. von Bonsdorff, B.: Zur Kenntnis der atypischen Amyloidose, Arb. a. d. path. Inst. d. Univ. Helsingfors **7**:369, 1933.

SUMMARY

Eleven cases of multiple myeloma with accompanying tumor-like deposits of amyloid in the striated muscles, and with amyloid in and about the joints, are recorded in the literature. The twelfth case is reported here.

In these cases amyloid was not abundant in the usual sites and frequently had atypical staining reactions.

Bence Jones protein was found in the urine in all the cases in which its presence or absence was recorded.

Clinically the involvement of the joints and muscles by the amyloid masses may simulate rheumatoid arthritis.

NOTE.—Since the case report presented in this article was submitted for publication, there was admitted to the wards of New York Hospital a 38 year old Negro with a history of arthritis involving the joints of both upper and lower extremities, of five years' duration. The deformity of the joints was striking. There were masses of firm to semifluctuant nodes varying from 1 to 10 cm. in diameter and, in addition, many firm subcutaneous nodules in the forearms. The tongue was larger than normal and showed ulceration along its margins. A biopsy of material from the sternum proved the existence of plasma cell myeloma in the bone marrow. Biopsy of the nodes in the forearm and tongue showed atypical amyloid deposits, with a staining reaction similar to that in the case reported. There was serious impairment of renal function, with marked albuminuria for the past year. Bence Jones proteinuria was observed inconstantly. The roentgenograms of all the bones closely resembled those in the case reported except that there was evidence of a destructive process in one vertebra. The results of examination of the blood were of interest: The congo red tests showed 60 per cent retention in the blood stream at the end of one hour; the amount of total proteins was elevated to 9.5 Gm. per hundred cubic centimeters, with the ratio of albumin to globulin 2.2 to 7.3; there was 12.4 to 13.7 mg. of calcium per hundred cubic centimeters, with 3.5 mg. to 4.5 mg. of phosphorus per hundred cubic centimeters; the uric acid amounted to 10 mg. per hundred cubic centimeters. There was severe secondary anemia.

The history of the past five years revealed that the patient had been treated at two other hospitals for an infectious arthritis of unknown origin. Low grade fever had been present almost constantly.

This case again illustrates the atypical nature of myeloma, with emphasis on arthritis as the clinical picture. The five year duration is noteworthy of the slow tempo of the disease process.

144 East Ninetieth Street.

Progress in Internal Medicine

GASTROENTEROLOGY

A REVIEW OF THE LITERATURE FROM JULY 1938 TO JULY 1939

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Scrutiny of this year's literature on the activity and disturbances of the alimentary tract reveals, as usual, material of purely physiologic interest, observations based on clinical investigation and actual studies of disease in relation to diagnosis or therapeusis. No attempt will be made to review the entire literature on gastroenterologic subjects, as it is too voluminous and many of the contributions are merely repetitive. Articles have been chosen with a view chiefly to their clinical application. Many important articles dealing with nutritional problems that bear on the function of the digestive tract have been considered outside the scope of this review.

ESOPHAGUS

Little new has been added to knowledge of the physiology or of the diseases of the esophagus. It is important, however, to note the continued interest in the surgical treatment of carcinoma of the esophagus, inasmuch as palliative treatment by irradiation or bougienage is for the most part extremely unsatisfactory. Since Torek's successful resection of the thoracic portion of the esophagus for cancer in 1913, 31 additional cases have been reported, and, of these, 18 during the past three years. Adams and his co-workers [1] attacked the problem experimentally and attempted to develop a surgical method consistent with a reasonable prospect of success. Resection of as much as 4 inches (10 cm.) of the thoracic portion of the esophagus with gastroesophagostomy was successfully performed in more than half of 13 experimental animals. This degree of success encouraged the authors to attempt a similar procedure in a patient with carcinoma of the thoracic portion of the esophagus. The operation was successfully performed, and the patient's convalescence was entirely uneventful. Such results are important in that they may eventually lead to a relatively safe standardized procedure that may be applied to what is usually considered an inoperable condition.

1. Adams, W. E.: Escudero Bueno, L.; Aronsohn, H. G., and Shaw, M. M.: Resection of Thoracic Esophagus: Clinical and Experimental Study, J. Thoracic Surg. **7**:605, 1938.

A rather unusual esophageal obstruction reported by Waltz [2] was due to ingestion of a hygroscopic gum laxative ("saraka"). One drachm (3.8 cc.) of the preparation was swallowed by the patient, and immediately afterward a second drachm was taken with only a small amount of water. Following the swallowing of the hygroscopic laxative, symptoms of esophageal distention and obstruction developed rapidly and were not relieved until the material was aspirated through an esophagoscope.

Seven cases of peptic ulcer of the esophagus are reported by Chamberlin [3] in an article in which the literature on the subject is summarized in a satisfactory fashion and the cause of the condition considered from a new angle, namely, the presence of a short esophagus or of a diaphragmatic hernia or of both. Previous authors dealing with the subject have laid particular stress on the presence of an aberrant gastric mucosa in the lower third of the esophagus, but none has mentioned the aforenamed conditions as contributing to the formation of an esophageal peptic ulcer. Chamberlin reports the results of both roentgenologic and esophagoscopic examinations, and in 6 of the 7 reported cases one or both of these abnormalities—a diaphragmatic hernia or a short esophagus—were present. It is of interest that Jackson, who has reported more cases of peptic ulcer of the esophagus than any other observer, made no report of the roentgen findings in his cases. While the subject is not new, the article is worthy of careful reading.

STOMACH

The entire subject of the physiologic control of gastric acidity has been approached by numerous investigators, and a little further knowledge has been added. This phase of gastric physiology is influenced by numerous factors, and studies regarding it are obviously of importance. Several of the immediate variables in the complicated physiology of the gastric juice have been enumerated by Hollander [4] and by Wilhelmj and Finegan.[5] Hollander mentions six factors of importance: admixture of saliva, regurgitation of intestinal contents, peptic secretion, secretion of a specific dilution factor, mucus secretion and reabsorption

2. Waltz, M. R.: Esophageal Obstruction Resulting from an Injudicious Method of Ingesting a Hygroscopic Gum Laxative (Saraka): Esophagoscopic Removal, J. A. M. A. **112**:229 (Jan. 21) 1939.

3. Chamberlin, D. T.: Peptic Ulcer of the Oesophagus, Am. J. Digest. Dis. **5**:725, 1939.

4. Hollander, F.: Factors Which Reduce Gastric Acidity, Am. J. Digest. Dis. **5**:364, 1938.

5. Wilhelmj, C. M., and Finegan, R. W.: The Gastric Secretory Curve Before and After the Mann-Williamson Operation, and Its Bearing on the Normal Regulation of Gastric Acidity, Am. J. Digest. Dis. **5**:373, 1938.

of hydrochloric acid. All of these must be considered in any attempt to evaluate the gastric secretory mechanism.

Factors Affecting Gastric Secretion.—Certain factors, many of which importantly affect gastric secretion, have been studied carefully. Schiff and associates [6] observed the effect of intramuscular injections of theelin (an estrogenic substance) and conclude in their report that even over long periods of time this substance has little or no effect on gastric acidity. Felson and Schiff [7] studied the effect on gastric secretion of the subcutaneous administration of the gonadotropic substance from the urine of pregnant women (antuitrin-S) in 7 persons. Daily doses of 1 cc. of the substance were given for a total of from 32 to 150 injections. No constant effects on the volume or the acidity of the gastric juice were noted.

The effect of acetylbetamethylcholine hydrochloride (mecholyl) was studied by Flexner and Wright [8] because of previous divergent reports following the use of this cholinergic drug. Rabbits and cats showed little or no change in the gastric acidity following the subcutaneous injection of mecholyl. Most human beings when proper care was taken to prevent swallowing of saliva showed a slight to marked rise in free and in total acidity following such an injection. There was an associated marked increase in the flow of saliva, which became mucinous and more alkaline.

The effect of continuous removal of gastric contents with resulting hypochloremia and alkalosis was studied by Lyall and Nicol.[9] Observations made on the gastric secretion under control conditions and during the conditions of the experiment revealed no significant changes in the composition of the gastric juice, even in the presence of marked changes in the chemical composition of the blood. There was some diminution in the total volume of gastric juice secreted.

A secretory depressant in the gastric juice itself has been reported by Brunschwig, Prohaska, Clarke and Kandel.[10] Their conclusions were reached during observations on the effect of intravenous injections of neutralized gastric juice in dogs. The intravenous injection of their own

6. Schiff, L.; Felson, H.; Graff, J., and Meyer, B.: Effect of Estrogenic Hormone on Gastric Acidity, Am. J. Digest. Dis. **5**:292, 1938.

7. Felson, H., and Schiff, L.: The Effect of Anterior Pituitary-like Hormone on Gastric Acidity in Man, Am. J. Digest. Dis. **5**:277, 1939.

8. Flexner, J., and Wright, I. S.: Effect of Acetyl-B-Methyl-Choline (Mecholyl) on the Gastric Secretion in Animals and in Man, Am. J. Digest. Dis. **5**:736, 1939.

9. Lyall, A., and Nicol, B. M.: The Gastric Secretions in Experimental Hypochloraemia, J. Physiol. **96**:21, 1939.

10. Brunschwig, A.; Prohaska, J. V.; Clarke, T. H., and Kandel, E.: A Secretory Depressant in Gastric Juice, read before the Central Society for Clinical Research, Nov. 4, 1938.

gastric juice or of that obtained from other animals produced no effect on gastric secretion. On the other hand, gastric juice obtained from patients with pernicious anemia and similarly treated produced in 9 animals out of 12 periods of achlorhydria. Similar material obtained from patients with cancer of the stomach resulted in temporary achlorhydria in 3 animals out of 6, whereas only 3 specimens obtained from patients with neither pernicious anemia nor cancer had any such effect. Boiling the "positive" juices for ten minutes destroyed the secretory depressant factor.

Day and Komarov [11] studied the effects of dextrose on the secretion of gastric juice in dogs. As found by previous investigators, the administration of hypertonic dextrose solutions (20 to 40 per cent) by the intravenous or intraduodenal route readily inhibited the gastric secretion provoked by sham feeding. Only a very concentrated solution (40 per cent) produced any appreciable inhibition of the secretion of the gastric juice evoked by rhythmic electrical stimulation of the vagi. Similarly, only moderate effects were noted on the secretion induced by the subcutaneous or intraduodenal administration of histamine, either with or without anesthetics. The authors advance the theory that the inhibitory effect of concentrated dextrose may be partly of central and partly of peripheral origin; in the latter case it is largely, if not entirely, due to changes in the osmotic condition of the body fluids.

Studies of gastric acidity in diabetic patients were carried out by Fenz [12] in a series of 116 patients. Anacidity (with a caffeine test meal) was found in practically half the patients and low acid content in about one sixth. Anacidity was more frequently found in untreated patients than in those receiving insulin and therefore could not be attributed to insulinization. The severity of the diabetes did not appear to determine the presence of anacidity, but it was noted that those patients who responded most readily to the administration of insulin were more apt to show anacidity. Of some interest is the finding that 44 of the 116 diabetic patients presented diarrhea, and of this group 70 per cent showed no free acid in the gastric contents. Of those with the most severe diarrhea, 80 per cent showed anacidity. The authors are inclined to believe that the diarrhea frequently noted in diabetic persons is most frequently gastrogenic in origin, although such a conclusion is open to some question.

An important and interesting study on gastric secretion was carried out by Seymour, Spies and Payne [13] in 40 persons with chronic

11. Day, J. J., and Komarov, S. A.: Glucose and Gastric Secretion, Am. J. Digest. Dis. **6**:169, 1939.

12. Fenz, E.: Ueber die Anazidität der Diabetiker, Wien. Arch. f. inn. Med. **32**:283, 1938.

13. Seymour, W. B.; Spies, T. D., and Payne, W.: Gastric Secretion in Chronic Alcoholic Addiction, J. Clin. Investigation **18**:15, 1939.

alcoholism. The volume of the gastric contents during fasting was 20 cc. or less in over 70 per cent of the subjects, and the consistency was noted as being very thick and ropy. Twenty minutes after the injection of histamine half of the subjects showed more than 20 cc. of limpid, clear gastric juice. Only 2 out of the entire group had free acid during fasting, but this varied after repeated injections of histamine, some of the subjects tending to show free acid after several injections had been given. Only 3 patients showed absence of pepsin from the gastric juice, and only 7 showed no rennin. The findings are definitely suggestive of the effect of prolonged use of alcohol on gastric secretion, inasmuch as the achlorhydria persisted even after discontinuance of the use of alcohol for an appreciable period of time in 13 patients. It should be noted that the duration of addiction was from seven to forty years. In this particular group it is striking that the subjects were singularly free from gastrointestinal complaints and presented no evidence of a deficiency disease. In addition to the foregoing observations, the authors show that the incidence of achlorhydria is even higher in persons with alcoholism who suffer from polyneuritis than in those with uncomplicated alcoholism.

Necheles and his group [14] undertook studies on gastric secretion in the presence of extragastric malignant tumor. Sixteen rabbits with Brown-Pearce tumors were studied in an attempt to substantiate the clinical observation that human beings with extragastric malignant tumors have diminished gastric acidity. No alteration in gastric acidity or pepsin was observed even in animals with extensive carcinoma. These findings, together with the observation that diminished gastric acidity may be present long before the appearance of the malignant tumor, and the fact that a higher incidence of achlorhydria and diminished gastric acidity occurs normally with advancing years lead the authors to believe that a reduction in acid secretion in the stomach in cases of extragastric malignant tumor has not been satisfactorily established.

The relationship between achlorhydria and the level of ascorbic acid in the blood has been studied by Alt, Chinn and Farmer.[15] Determinations of ascorbic acid were made in 44 cases of achlorhydria associated with pernicious anemia or iron deficiency. With diets adequate in vitamin C, the plasma levels remained significantly below normal in patients with pernicious anemia but not in the iron deficiency group. With diets inadequate in vitamin C, the plasma values decreased in both groups to well below the normal control levels. The cause of this

14. Necheles, H.; Appel, M.; Wald, D., and Olson, W.: Gastric Secretion in Extragastric Malignancy, Am. J. Digest. Dis. **6**:261, 1939.

15. Alt, H. L.; Chinn, H., and Farmer, C. J.: Blood Plasma Ascorbic Acid in Patients with Achlorhydria (Pernicious Anemia and Iron Deficiency Anemia), Am. J. M. Sc. **197**:229, 1939.

apparent variation in behavior between patients with pernicious anemia and those with iron deficiency anemia is not immediately obvious, but the mucosal changes characteristic of pernicious anemia with the associated changes in intestinal absorption may account for the differences observed.

The relationship of gastric motility to anorexia was studied by Gulliksen and collaborators.[16] Of 200 children studied, 13 had a very low intake of food with moderately or definitely poor appetites. Records of the hunger contractions in this group of undernourished, anoretic children showed that they had a greater number of contractions and a shorter interval between periods of activity and that the hunger contractions were less vigorous in height and duration than those observed in children with hearty appetites. The authors suggest that the small appetites in such children may be due to lack of normal sensations of hunger.

Beyer and Meek,[17] in experiments on human beings, confirm the previous observations that benzedrine sulfate decreases the initial emptying time of the stomach but increases the period of final emptying. The experiments indicate that the decrease in initial emptying time is due to a primary increase in tonus and activity of the stomach, raising intragastric pressure and forcing the contents through a pylorus the tonus of which, if altered by the drug, may be only slightly increased. The delay in the final emptying is due to secondary inhibition of the gastric musculature with an increase in pyloric tonus. The results suggest that whatever value benzedrine sulfate has in overcoming functional pylorospasm of a moderate degree is due to the initial stimulation of the gastric musculature, which overcomes the pyloric resistance, rather than to any direct inhibiting effect on the tonus of the pylorus.

Effects of Smoking.—Several articles on the effect of tobacco smoking on the physiology of the alimentary tract are of interest. An article by Schnedorf and Ivy,[18] although containing no new material, offers a good summary of previously described experiments and an excellent commentary. Schnedorf and Ivy noted the effects of smoking on salivary secretion in 15 chronic smokers and 5 nonsmokers. They observed the effects on the emptying time and the acidity of the gastric contents in 7 smokers without organic disease and in 22 smokers suffer-

16. Gulliksen, D. P.; Fogelberg, A., and Kardos, L.: Anorexia and Gastric Motility, Am. J. Digest. Dis. **5**:814, 1939.

17. Beyer, K. H., and Meek, W. J.: Effect of Benzedrine Sulfate on Gastric Emptying and Intestinal Activity, Arch. Int. Med. **63**:752 (April) 1939.

18. Schnedorf, J. G., and Ivy, A. C.: The Effect of Tobacco Smoking on the Alimentary Tract: Experimental Study of Man and Animals, J. A. M. A. **112**: 898 (March 11) 1939.

ing from peptic ulcer. Smoking reflexly stimulated salivary secretion in most of these subjects and inhibited hunger contractions of the stomach. It was found that when it has any effect on the stomach it tends to depress gastric secretion and retard evacuation. Only in occasional persons does it tend to cause significant changes in the gastric contents or an increase in gastric acidity. Incidentally, it tends to augment the motility of the colon but affects biliary and pancreatic secretion only when there are marked variations in the blood pressure. The authors conclude that only as a person approaches the limit of his tobacco tolerance do undesirable changes take place in the activity of the alimentary tract. All patients with peptic ulcer or with clonic disturbances who smoke should be cautioned regarding the undesirable effects of straining their tolerance to tobacco. Schnedorf and Ivy are unwilling to interpret any of their data as directly indicating that smoking has any beneficial effect on the digestive tract. Although they are quite properly cautious in the interpretation of their findings, a careful reading of their article is justified inasmuch as they contribute a rather timely and sound approach to the question of smoking in relation to digestive disturbances.

Two articles by Short and co-workers [19] are also of interest. The first article represents an analysis of observations on 2,031 persons, of whom 1,292 were habitual smokers, in relation to symptoms referable to the respiratory, circulatory, gastrointestinal and nervous systems. In all of these systems the symptoms were increased among the smokers. The frequency of "heartburn" was increased by 100 per cent over that observed in the nonsmokers, and other digestive disturbances were noted to be increased in similar percentages. The statement that "the relation of tobacco smoking to gastric disturbances, especially hyperacidity, is a frequent clinical observation" is of interest in relation to their second article, which gives a direct comparison of the reaction of the human system to tobacco smoking and to epinephrine. Their observations confirm the view that the characteristic effects of tobacco smoking on the pulse, blood pressure, peripheral cutaneous temperature and blood sugar can be explained by an increased output of epinephrine, which is due most probably to the stimulative effect of nicotine on the sympathetic nerve–epinephrine system. The authors might have added that "heartburn" and so-called hyperacidity could also be explained properly by overstimulation of the sympathetic nerve fibers controlling the lower end of the esophagus.

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19. Short, J. J.; Johnson, H. J., and Ley, H. A.: Effects of Tobacco Smoking on Health: Study of 2,031 Medical Records, J. Lab. & Clin. Med. **24**:586, 1939. Short, J. J., and Johnson, H. J.: Direct Comparison of Reactions of Human System to Tobacco Smoke and Adrenalin, ibid. **24**:59, 1939.

Peptic Ulcer.—The etiologic nature of this chronic disease is still undetermined, although studies regarding the effect of lesions of the brain, alterations in hormonal activity and abnormal functioning of the autonomic nervous system continue to be of interest. Further evidence that discrete intracranial lesions may be the cause of ulceration of the upper part of the digestive tract is found in observations made by Opper and Zimmerman,[20] who obviously have been stimulated by the previous studies of Cushing. These authors showed erosions in the esophagus, stomach or duodenum in 21 cases of lesions of the brain. The changes in the brain were of various etiologic character and variously localized in the midbrain, interbrain and cortex. They feel that gastrointestinal lesions in cases of cortical and mesencephalic involvement are most probably mediated through the hypothalamic nuclei.

Gauss [21] also presents an interesting analysis of 20 cases of gastrointestinal symptoms in association with intracranial disease. In his series no ulcerations of the digestive tract were demonstrated, but his comments as to the genesis of digestive symptoms in relation to intercranial disease are stimulating. He attempts to subdivide the symptoms in these cases into three groups. The first group, including the commonest symptoms, classified as dyspeptic, includes nausea, vomiting, abdominal distress and changes in appetite in association with tumor of the brain. A second group of symptoms, classified as paroxysmal, is associated with the sensory and motor disturbances common to epilepsy, migraine and syphilis. A third and small group is that of the true peptic ulcer syndrome, which may occur at times in association with a tumor or other expanding intracranial lesion. He emphasizes the obvious wisdom of considering the possibility of a lesion of the brain when there are otherwise unexplained persistent disturbances of appetite and abdominal distress (with or without nausea and vomiting) not related to the normal gastric cycle. He also makes the important point that digestive symptoms of central origin are mediated by way of the lower levels of the central nervous system and hence have no localizing value.

In view of the publicity in the lay press attached to the treatment of ulcer with an extract of the posterior lobe of the pituitary, reported by Metz and Lackey,[22] it is important to comment on their work. Following a preliminary report in 1937, these authors present observations on 28 persons suffering from peptic ulcer. They report complete

20. Opper, L., and Zimmerman, H. M.: Ulcers of Digestive Tract in Association with Cerebral Lesions, Yale J. Biol. & Med. **11**:49, 1938.

21. Gauss, H.: Gastrointestinal Symptoms in Disease of the Brain, J. A. M. A. **112**:701 (Feb. 25) 1939.

22. Metz, M. H., and Lackey, R. W.: Peptic Ulcer Treated by Posterior Pituitary Extract: Two Years' Experience, Texas State J. Med. **34**:214, 1938.

symptomatic relief in 24 of the patients within three weeks after the start of treatment with a fresh preparation of the posterior lobe of the pituitary, administered hypodermically, orally or intranasally. The last route was preferred. The authors refer to previous studies on the influence of hypophysial extract on gastric secretion and adhere to the hypothesis that many patients with peptic ulcer exhibit pituitary deficiency. This assumption is largely based on the fact that 15 of their patients had definite polyuria and nocturia and responded more or less satisfactorily to the treatment. That the administration of posterior pituitary extract produced only a temporary healing effect on the ulcer is obvious from their statement: "Recurrences of ulcer healed under pituitary administration are to be expected, since this therapeutic agent probably relieves temporarily a deficiency." It is still too early to evaluate the results of such medication, and one is forced to recall the fact that almost any striking method for the treatment of peptic ulcer has always been of transient benefit. At the present time it will be wise to regard this latest addition to the therapy of ulcer as an interesting attempt to correlate certain known clinical facts with the manifestations of a chronic disease.

In this connection another important study has come from Sandweiss and collaborators [23] on the relation of gonadotropic hormones to peptic ulcer. These authors find, as have others, that pregnancy appears to have a beneficial effect on the symptoms of ulcer, and an examination of the records of 70,130 pregnant women consecutively admitted to hospital showed that only 1 had peptic ulcer. A high incidence of endocrinopathies, they thought, was found in 30 women with ulcers. Observations seemed to show that the symptoms of peptic ulcer are aggravated during the menopause. In addition to these clinical observations, studies were made on animals, a continuation of work reported last year. Of 34 Mann-Williamson dogs which had received daily injections of varying doses of the gonadotropic substance found in the urine of pregnant women (antuitrin S) and which had died, 50 per cent had no ulcers and 20 per cent had ulcers in the process of healing. Seventy per cent of the animals were therefore benefited during these injections. Ninety-eight per cent of the control Mann-Williamson dogs died of jejunal ulcers. The average time of survival of the control Mann-Williamson dogs was fifty-eight days, and the average of those treated with the gonadotropic factor was over one hundred days. In an attempt to produce similar results in human beings, 18 patients with active symptoms of peptic ulcers proved to be present were treated with daily injections of from 2 to 5 cc. of the same gonadotropic substance for a

23. Sandweiss, D. J.; Saltzstein, H. C., and Farbman, A. A.: Relation of Sex Hormones to Peptic Ulcer, Am. J. Digest. Dis. **6**:6, 1939.

period of fourteen consecutive days. Fourteen of the patients were benefited, but with commendable caution Sandweiss limits his enthusiasm to the suggestion that "in the dosage used, Antuitrin-S produces no more beneficial effects than other parenteral products." No effect on the free or total acid secretion was noted following daily subcutaneous injections of from 2 to 5 cc. of the substance. A note at the end of the article is probably important, stating that "preliminary observations on 20 Mann-Williamson dogs indicate that (*a*) urine from normal individuals contains a 'protective factor' against Mann-Williamson ulcers; and (*b*) this 'protective factor' is definitely absent from the urine of patients with peptic ulcer." The significance of these findings is still not clear, but there is little doubt that further careful investigations on the effect of endocrine secretions on normal and pathologic gastric function will be of interest.

As in previous years, numerous isolated experiences are noted regarding the cure or relief of peptic ulcer following unusual procedures. One such article is that reported by Bagdasarov and co-workers.[24] They repeatedly transfused whole blood from goats to 82 patients with ulcers. The transfusions were performed at intervals of two to four days at first and subsequently at five to seven day intervals, 3 to 12 cc. of blood being employed. Severe reactions were present in 8 per cent, and mild reactions were noted in nearly all patients so treated. Reactions typical of immediate and delayed allergic responses were not infrequently alarming. In spite of these reactions to transfusions of heterogenous blood, no fatalities were noted, and cures are claimed in about half of the cases followed. Although the findings are not without interest, one can hardly feel any enthusiasm about the method, especially as the authors point out seven absolute contraindications and three relative contraindications to its use.

Another new method for the treatment of ulcer is that described by Okada and Doi.[25] These workers obtained extracts from the mucosa of the stomach and duodenum that are said to contain all the essential parts of each mucosa and to have a regenerating effect specific for the mucosa of each of the portions, respectively, of the digestive tract. Preparations of these extracts were administered intravenously in 60 cases, a full course of treatment consisting of thirty injections. The vast majority of both patients with ulcer and patients with other gastric troubles treated with either gastric or duodenal extracts were "cured" or showed improvement, and the authors claim that the late results were

24. Bagdasarov, A. A.; German, K. A.; Gutson, G. I., and Zubelevich, M. M.: Hétérotransfusion du sang dans le traitement de l'ulcère gastro-duodénal, Acta-med. U. R. S. S. **1**:497, 1938.

25. Okada, S., and Doi, T.: Sur une nouvelle méthode de traitement de l'ulcère de l'estomac et du duodénum, Arch. d. mal. de l'app. digestif. **28**:935, 1938.

favorable. The results suggest those obtained by the use of histamine and should be subject to the same objections. Because of the frequency of favorable results from any parenteral treatment, one is inclined to be skeptical of the specific value of the aforementioned treatment and to recall the fact that in most instances an uncomplicated ulcer heals readily with any form of treatment within thirty days.

The majority of articles dealing with the treatment of patients with peptic ulcer are concerned with various modifications of already well established medical or surgical procedures. Of modifications in medical therapy, the majority, as usual, are concerned with measures directed toward reducing gastric acidity. By far the greatest attention has been paid to the use of colloidal aluminum hydroxide. Emery and Rutherford,[26] for example, like most writers, have found that symptoms of ulcer appear to be readily relieved by the administration of this substance, without any interference with the acid-base balance. They think that there may be some slight absorption from the gastrointestinal tract but feel that this preparation avoids all danger of producing alkalosis. They at first employed the continuous drip method of Woldman, but subsequently found that in most instances the oral administration of the drug was efficacious, an important point inasmuch as it simplifies the entire procedure for the average patient. It is quite probable that the drip method of treating ulcer is applicable only to those patients who fail to respond to other measures, and these authors' experiences are similar to those of almost all observers.

The beneficial effect of aluminum hydroxide gel appears to depend almost entirely on its action on gastric acid. Quigley, Einsel and Meschan [27] administered massive doses of the preparation to dogs for seventy-nine days without any significant effect on the time of gastric evacuation or on the histologic structure of gastric tissue, and the gastric secretory response to histamine was only transiently reduced. Ordinary amounts failed to produce any significant change in the motility or tone of the stomach or pyloric antrum. The authors believe that in human beings the reaction is similar but that in the presence of ulcer or other pathologic changes in the stomach the preparation might have additional effects on gastric evacuation and secretory activity.

Fauley, Ivy and collaborators [28] were unable to demonstrate on the basis of animal experimentation any prophylactic value of aluminum

26. Emery, E. S., Jr., and Rutherford, R. B.: Studies on the Use of Aluminum Hydroxide Gel in the Treatment of Peptic Ulcer, Am. J. Digest. Dis. **5**:486, 1938.

27. Quigley, J. P.; Einsel, I. H. and Meschan, I.: Some Effects Produced in the Normal Stomach by the Ingestion of Moderate and Massive Quantities of Aluminum Hydroxide Gel, J. Lab. & Clin. Med. **24**:485, 1939.

28. Fauley, G. B.; Ivy, A. C.; Terry, L., and Bradley, W. B.: An Attempt to Prevent Postoperative Jejunal Ulcer by Aluminum Hydroxide Therapy: An Experimental Study in Mann-Williamson Dogs, Am. J. Digest. Dis. **5**:792, 1939.

hydroxide in the prevention of jejunal ulcers in Mann-Williamson dogs. In spite of the fact that large doses and a large series of animals were used, there was no evidence that the administration of aluminum hydroxide prevented the occurrence of jejunal ulcers. As a matter of fact, the authors expressed the belief that the medication caused a decrease in appetite with a resultant diminution in food intake and a more rapid loss of weight. They suggest that its use be avoided in patients suffering from peptic ulcer complicated by a relative pancreatic and biliary insufficiency or a gastroenterostomy.

Reports on the control of gastric acidity by magnesium trisilicate continue to appear, typical reports being those of Reid [29] and Tidmarsh and Baxter.[30] The latter authors found that the addition of atropine and phenobarbital to magnesium trisilicate was of therapeutic value in that it brought about more restful nights, less apprehension and normal intestinal function.

The entire question of antacid therapy as related to peptic ulcer has been reviewed in an excellent article by Adams.[31] His review of the subject discloses nothing new but brings the entire matter up to date and presents it critically. There is a consideration of twenty-four substances that are administered orally to combat gastric acidity in the treatment of ulcer, in addition to comments on the use of mucin and hydrogen peroxide. The advantages and disadvantages of using these various substances are discussed with due regard to the chemical or physical activity of each and any unpleasant symptoms that may follow its use. The details of the pharmacologic action of each are presented. From the entire list Adams chooses colloidal aluminum hydroxide as the most appropriate medicament available at the present time for the control of gastric acidity.

An article by Eisele [32] on changes in the acid-base balance during alkali treatment for peptic ulcer also presents nothing new but is more or less clarifying as far as a complete summary of the various occurrences associated with alkaline therapy is concerned. He points out succinctly the facts pertinent to the use of alkali, namely, that an occasional patient may sustain injury to the kidneys from alkali therapy

29. Reid, C. G.: The Control of Gastric Hyperacidity by Magnesium Trisilicate, Am. J. Digest. Dis. **6**:267, 1939.

30. Tidmarsh, C. J., and Baxter, R. G.: Magnesium Trisilicate in Treatment of Peptic Ulcer, Canad. M. A. J. **39**:358, 1938.

31. Adams, W. L.: A Crictical Evaluation of Gastric Antacids, Arch. Int. Med. **63**:1030 (June) 1939.

32. Eisele, C. W.: Changes in the Acid-Base Balance During Alkali Treatment for Peptic Ulcer: Clinical Analysis of Alkalosis in Twenty-Eight Patients, Arch. Int. Med. **63**:1048 (June) 1939.

and that almost certainly a preexisting renal disease will be aggravated by this form of treatment. He shows that during the treatment with alkalis the work of the kidneys is greatly increased. In effect, he presents a good argument for the use of other forms of antacid.

A very timely and pertinent short article is that of Hollander [33] on effective neutralization of gastric contents. In a few lines Hollander presents more clearly than is usually done the important considerations in regard to antacid therapy. He points out that the important consideration is the influence of the p_H of gastric juice on peptic activity. For the neutralization of free acidity a terminal p_H of about 3 or 3.5 is generally accepted, although complete neutralization of gastric acidity requires elevation of the p_H to at least 7. Hollander calls attention to the fact that the "acid-pepsin" factor is the major one in the genesis of peptic ulcer and that an effective reduction in gastric acidity minimizes the influence of this factor. For this purpose, however, the attention must be focused on acidity in relation to pepsin activity rather than solely on the figures for acid dilution. Peptic activity practically ceases at a p_H of 4.5 to 5. Complete neutralization of all organic acids is not necessary, nor does it offer any additional benefits, and Hollander suggests that, in contradistinction to the free acidity end point and the total acidity end point as a critical value in antacid therapy, there be introduced the proteolytic neutralization point, i. e., the p_H at which digestion of protein in the stomach is reduced to a minimum.

A statistical study of a large number of analyses of gastric content (2,877) is of some interest in this connection. The greater part of the article is given to a discussion of the significance of gastric acidity after stimulation by histamine with comments on the wide variation in values. One of the conclusions of the authors (Ruffin and Dick [34]) is probably an important one in regard to the diagnostic value of gastric analysis. They state that if free hydrochloric acid is present after stimulation with histamine, the actual level of acidity is of little, if any, diagnostic significance. In other words, the authors by inference suggest that much of the diagnostic value of gastric analysis has been overemphasized. They also point out that the range of gastric acidity after histamine stimulation in normal persons is so great that it is impossible to determine what values are to be taken as evidence of normal acidity, hyperacidity or hypoacidity. In this series the incidence of achlorhydria

33. Hollander, F.: What Constitutes Effective Neutralization of Gastric Contents? Am. J. Digest. Dis. **6**:127, 1939.

34. Ruffin, J. M., and Dick, M.: The Significance of Gastric Acidity After Histamine Stimulation: A Statistical Study of 2,877 Gastric Analyses, Ann. Int. Med. **12**:1940, 1939.

in normal controls compares closely with the findings of others. A particularly interesting finding is that 24 patients (5.4 per cent of the series) with active duodenal ulcers, as shown by x-ray pictures, had no free acid after stimulation with histamine.

A series of reports have appeared relating to the level of ascorbic acid in the blood of patients with peptic ulcer. No new facts have been presented, however, following the original finding that, along with other conditions that are associated with a limitation of diet, the plasma values for vitamin C are low. Some interest attaches to the report by Warren, Pijoan and Emery,[35] which summarizes studies of vitamin C saturation in a small group of patients with active duodenal ulcer. It was found that these patients utilized 20 per cent more ascorbic acid than do normal persons. There was no evidence that they were unable to absorb the drug when it was given by mouth. These authors point out an important fact: that the usual Sippy diet contains much less than the normal requirement of vitamin C, but they do not feel that evidence exists at present that vitamin C therapy has any direct healing influence on ulcer.

The use of pectin as prophylactic and curative of experimental ulcers in animals was studied by Winters, Peters and Crook.[36] A control group of dogs were treated with cinchophen, and typical ulcers were produced in each instance. Of 9 dogs similarly treated except for the addition of pectin to their diet, 8 did not acquire ulcers. Two animals which were proved by operation to have cinchophen ulcers were subsequently treated with both cinchophen and pectin. These animals were put to death on the twenty-first and twenty-fifth days, respectively, after operation, and postmortem examinations showed well healed ulcers. Further reports as to the value of pectin in the therapy of ulcer, especially in human beings, are needed in determining whether this preparation constitutes an addition to the present armamentarium for the treatment of ulcer.

The appearance of a large number of articles on the treatment of bleeding ulcer is evidence of a renewed interest in the optimum treatment for the patient suffering from a massive hemorrhage. There is a wide divergence of opinion as to the details of therapeutic measures, but there can be little doubt that the experience of most observers warrants the assumption that such patients should be treated by medical measures except on rare occasions. There is general agreement as to

35. Warren, H. A.; Pijoan, M., and Emery, E. S., Jr.: Ascorbic Acid Requirements in Patients with Peptic Ulcer, New England J. Med. **220**:1061, 1939.

36. Winters, M.; Peters, G. A., and Crook, G. W.: Pectin as a Prophylactic and Curative Agent for Peptic Ulcers Produced Experimentally with Cinchophen, Am. J. Digest. Dis. **6**:12, 1939.

the fact that massive hemorrhage from an ulcer involves relatively slight risk when the patient is under the age of 45 years, and the vast majority of observations lead one to the conclusion that the policy of withholding food from a patient with a bleeding ulcer is definitely unwise. Various modifications of Meulengracht's liberal dietary regimen are reported, but the fundamental principles of small frequent feedings of simple food instituted without delay after a massive hemorrhage seems to be agreed on with few exceptions. It is probable that the details of the dietary regimen in such an emergency are of relatively minor importance. There is rarely a patient in the younger group and a slightly larger percentage of the patients over the age of 45 years for whom surgical measures must be considered. The danger of a gastric surgical operation in the presence of massive hemorrhage is so great, however, that the decision to operate should be reached only after a careful consideration of the patient's case by both the physician and the surgeon. When surgical measures are indicated, they should not be delayed beyond forty-eight hours after the original hemorrhage. An excellent discussion of the surgical aspects of the problem is presented by Pfeiffer,[37] and a clear exposition of the difficulties in deciding on such an emergency operation is added by Miller and Elsom [38] from the point of view of the internist.

Statistics on the actual mortality from bleeding ulcer still leave much to be desired. Hesser [39] reports an interesting series which includes 122 cases of ulcer with 2 or more hemorrhages. In this group of cases of ulcer with recurrent hemorrhages there were only 4 deaths, 3 of which occurred in patients over the age of 60. Herlihy [40] presents a report of twelve months' experience with Witts' modification of Meulengracht's routine. No patients were operated on, and there was a mortality of 4 per cent. He stresses the important point of not handing the surgeon a "forlorn hope."

An important article is that of LaDue,[41] as it refers back to the original work of Lenhartz, in 1906, who gave an egg albumin and milk diet immediately after hemorrhage in 146 cases, with a mortality of 2.14 per cent. LaDue's work properly gives credit to Andresen,

37. Pfeiffer, D. B.: Gastric Hemorrhage, J. A. M. A. **111**:2198 (Dec. 10) 1938.

38. Miller, T. G., and Elsom, K. A.: The Management of Massive Hemorrhage from Peptic Ulcer, M. Clin. North America **22**:1711, 1938.

39. Hesser, S.: Relapsing Gastric Hemorrhages and Their Treatment, Acta med. Scandinav. **98**:340, 1939.

40. Herlihy, J. D.: Immediate Feeding in Hematemesis and Melena, M. J. Australia **2**:996, 1938.

41. LaDue, J. S.: Treatment of Massive Hemorrhage Due to Peptic Ulcer, Arch. Int. Med. **63**:1017 (June) 1939.

whose report in 1927 of the treatment of bleeding ulcer by dietary measures should have received much more attention than it has. Andresen's methods have been carried out by LaDue, who states that in principle they correspond to those subsequently introduced by Meulengracht. Transfusion by the gravity drip method is accepted by most authors as a valuable and important adjunct to the treatment of patients with bleeding ulcer. It is rather surprising to note, however, that in LaDue's report, based on Andresen's teaching, transfusion and the intravenous administration of fluids are considered to be contraindicated. This is not in accordance with the experience of most writers, who are convinced that drip transfusion does not cause any appreciable rise in blood pressure and is beneficial rather than otherwise.

Browne and McHardy [42] report on 131 patients with bleeding ulcers, showing a mortality in those treated medically of 3.4 per cent. They do not advocate the immediate institution of feeding after hemorrhage. They recommend the continuous aluminum hydroxide drip method suggested by Woldman as the treatment of choice during the first few days after hemorrhage. Crohn and Lerner [43] agree as to the value of conservative medical treatment for such patients but state that their experience with Meulengracht's diet has not been encouraging. They still prefer starvation during the early period of treatment.

Further experiences in the treatment of this frequent complication of ulcer are required before a complete evaluation of the details of medical management can be obtained, but the present indications are that some modification of the principle of frequent small feedings of simple food given immediately after hemorrhage has ceased will be found advisable. Whether the generous dietary permitted by Meulengracht is preferable to the more limited one advocated by Andresen, consisting essentially of gelatin and cereals, remains to be seen. At present many authors prefer the administration of vitamin C as an adjunct to the medical treatment of the patient with bleeding ulcer, but it is generally admitted that there is no satisfactory evidence as yet that this form of therapy is rational.

Attempts are still being made to study the retention of nitrogen and the high blood urea following massive gastrointestinal hemorrhage. Little new has been added to Christiansen's work, but a report by Borst [44] is of some interest. This author gives a detailed study of 3

42. Browne, D. C., and McHardy, G.: Management of Peptic Ulcer Hemorrhage, Am. J. Digest. Dis. **6**:87, 1939.

43. Crohn, B. B., and Lerner, H. H.: Gross Hemorrhage as a Complication of Peptic Ulcer, Am. J. Digest. Dis. **6**:15, 1939.

44. Borst, J. G. G.: Hyperchloremia and Hyperazotemia in Patients with Recurrent Massive Hemorrhage from Peptic Ulcer, Acta med. Scandinav. **97**:68, 1938.

patients with gross hemorrhage showing retention of nitrogen and chlorides in the blood and a low level of chlorides in the urine. The retention of nitrogen is attributed to an increased formation of urea from the blood in the intestinal tract. The concentration of urea in the urine remains high until the blood volume is restored. During posthemorrhagic dilution of the blood the kidneys excrete neither sodium nor chloride, with the result that if sodium chloride is given, the plasma chlorides rise markedly above normal, with excessive amounts of potassium being excreted in the urine. He advocates drip transfusions for the purpose of restoring red blood cells and plasma protein and the administration of fluids at the same time until the concentration of urea in the urine drops below maximum and the chloride content rises. He also advocates the determination of urea clearance as the best method of measuring the severity of the shock. Although the findings corroborate the results of previous studies and are of interest, it seems possible that too much therapeutic and prognostic importance has been assigned to this interesting phenomenon of nitrogen retention following gross hemorrhage. Clinical experience seems to suggest that simple determinations of red blood cells, hemoglobin and fluid balance plus close observation of the pulse and blood pressure are preferable and more reliable criteria for determining treatment and prognosis than these more complicated measures.

Black [45] corroborates the evidence for a lowering of urea clearance in this condition and states that in the 12 cases which he studied the urea clearance rose to normal within a week after the hemorrhage. He believes that there is some correlation between red cell volume and urea clearance and that his estimations indicate some degree of impairment of renal function, although present evidence is insufficient to establish definitely the mechanism of the renal impairment.

Dill and Isenhorn [46] present observations as to the incidence and cause of fever in patients with bleeding peptic ulcer. Two hundred male patients who were proved to be suffering from peptic ulcer were studied, and 53 per cent were found to have a slight elevation of temperature (over 99 F.). Of the group with bleeding ulcers, 80 per cent were febrile, whereas only 46 per cent of the patients with nonbleeding ulcers had an elevated temperature. In a group of patients without demonstrable organic disease, 37 per cent of the patients showed evidence of some elevation of temperature (i. e., 99 F. or above for more than two days, 99.2 F. or above for two days, or any single rise above 100 F.). A comparison of these with the patients who had ulcer showed that the latter

45. Black, D. A. K.: Urea Clearance in Hematemesis, Lancet **1**: 323, 1939.

46. Dill, L. V., and Isenhorn, C. E.: Observations in Incidence and Cause of Fever in Patients with Bleeding Peptic Ulcers, Am. J. Digest. Dis. **5**:779, 1939.

presented an elevation of temperature more frequently than patients without demonstrable organic disease, a tendency increased by hemorrhage. Anemia, with or without evidences of gross hemorrhage, seems to increase the tendency toward a slight elevation of temperature. The conclusion reached by the authors that the absorption of blood degradation products plays little part in the production of fever seems rather unwarranted, however, in view of their own observations and those of others. Their suggestion that patients with gastric neuroses are relatively prone to slight elevations of temperature is of interest and is probably correct.

In view of the foregoing findings the report of Demole and Perret [47] regarding the speed of sedimentation of red cells in cases of gastroduodenal ulcer is of some interest. Using Westergren's technic, they studied 102 cases. There was a normal sedimentation rate in 80 per cent of the cases of simple uncomplicated gastroduodenal ulcer; the rate was accelerated in 63 per cent of the cases of ulcer complicated by stenosis, penetration or bleeding. A point of interest is that gross hemorrhage apparently does not cause immediate acceleration of the sedimentation rate. The authors obviously suggest that an elevated sedimentation rate should make one suspicious that complications have arisen in an otherwise simple ulcer.

The surgical treatment of peptic ulcer is still somewhat unsettled, the divergent points of view ranging from those of Finsterer and Berg to those of more conservative surgeons. It will be worth while to suggest the soundness of the point of view expressed by Cutler,[48] who comments on the type of operation to be employed in cases in which surgical intervention is indicated. In a review of the surgically treated patients at the Roosevelt Hospital between the years 1934 and 1937, the following guiding principles in the choice of operation have been evolved: (1) The operation must be of such a nature that the particular patient can tolerate and survive it; (2) not only should it aim at the alleviation of symptoms, but it should give freedom from the likelihood of complications, both early and late; (3) the ideal procedure having been determined, it should be abandoned at operation if the condition warrants it. One might add as a fourth desideratum that a final decision for or against surgical intervention should rest on a balancing of risks, namely, the risk of operation as opposed to the risk of a continuation of non-

47. Demole, M., and Perret, P. E.: Notions statistiques sur la vitesse de sédimentation dans l'ulcère gastro-duodenal, Arch. d. mal. de l'app. digestif **29**:194, 1939.

48. Cutler, C. W., Jr.: Changing Methods in Surgical Treatment of Peptic Ulcer: Study of Cases Operated upon at Roosevelt Hospital, New York, Ann. Surg. **108**:68, 1938.

surgical measures. The type of surgical procedure to use in the treatment of peptic ulcer must always remain an individual decision in a given case.

Most authors who are experienced in the treatment of peptic ulcer will be in general agreement with the conclusions expressed by Allen and Welch,[49] who point out the marked change in such therapy during the past twenty years. Prompt surgical intervention is indicated for the patient in whom acute perforation develops and is occasionally required in an episode of massive bleeding. Thorough medical care is indicated for all others. Patients in whom cicatricial obstruction of the pylorus develops do well with gastroenterostomy; those in whom ulcers develop which are intractable to medical care or which have been associated with massive hemorrhage should receive subtotal gastrectomy. That a gastroenterostomy is still the operation of choice in a few of the older "poor risk" patients is the opinion of most conservative physicians and surgeons, and in patients thus treated, even in the absence of obstruction, favorable results are usually obtained.

As a commentary on the futility of ill advised surgical treatment, the report of Finsterer [50] is important. He reviews his own surgical results in 331 patients (of 2,753) on whom previous operations had been performed for the relief of symptoms of ulcer. Exclusive of operations for acute perforation, acute hemorrhage or gastrocolic fistula his mortality figure was 8.6 per cent. The operation most frequently performed prior to that done by the author was gastroenterostomy (in 190 patients), with a subsequent failure of the original ulcer to heal or the formation of a jejunal ulcer. Six and eight tenths per cent of those patients who previously had undergone gastroenterostomy died as a result of further surgical operation, whereas the mortality from an operation after a previous resection was 23.5 per cent. Finsterer states that the occurrence of a jejunal ulcer after a radical resection of the stomach is always due to technical faults, an indication for extreme caution in advising this radical procedure.

The necessity for special care of the "poor risk" patient is being more clearly recognized by physicians and surgeons alike. When surgical treatment is indicated, the preoperative and postoperative nutrition may be of paramount importance in the reduction of mortality and the avoidance of postoperative complications, such as nutritional edema at the site of operation. For this reason the closest collaboration between the physician and the surgeon is necessary for the production of optimum

49. Allen, A. W., and Welch, C. E.: Peptic Ulcer Considered from a Surgical Point of View, New England J. Med. **220**:103, 1939.

50. Finsterer, H.: Results of Repeated Operations on the Stomach, Surg., Gynec. & Obst. **68**:334, 1939.

results, a fact that is universally recognized by the most experienced surgeons. Attention has recently been directed toward this phase of the surgical management of ulcer by such men as Ravdin [51] in this country.

In a discussion of recurrent peptic ulceration after gastric operation Kelly [52] specifically emphasizes the importance of the avoidance of all kinds of rigid starvation before and after any operative procedure, and several methods of postoperative feeding are introduced. Of these, a jejunostomy accompanying or following the original operation or the introduction of a double lumen tube through the stoma into the jejunum at the time of operation, as advocated by Abbott and Rawson,[53] deserves serious consideration.

The parenteral administration of vitamins as an adjunct in these difficult cases has been stressed by various authors, and particular stress has been laid on the need for vitamin B complex and for vitamin C. A specific indication for the use of the latter preoperatively and postoperatively was originally suggested by the work of Lanman and Ingalls and has been further emphasized by the recent work of Bartlett, Jones and Ryan,[54] who show that apparently there is a striking need for ascorbic acid during the early period of wound healing immediately after operation.

The necessity for adequate amounts of protein in these patients is generally recognized, but so far the problem of supplying it has been only partially solved by the use of frequent blood transfusions. In this connection the work of Elman and Weiner [55] is of extreme interest and leads to the hope that eventually some preparation will be evolved which contains adequate amounts of nitrogenous material and which can be administered intravenously. These authors are the first to report the intravenous administration of a mixture of amino acids to human beings as a means of parenteral protein alimentation. The mixture was obtained by the addition of 2 per cent tryptophan and cystine to the product of acid hydrolysis of casein. No evidence of toxicity was observed if the injections were given slowly. The injected animo acids were rapidly

51. Ravdin, I. S.; Stengel, A., Jr., and Reigel, C.: The Control of Hypoproteinemia in Surgical Patients, J. A. M. A., to be published.

52. Kelley, R. E.: Recurrent Peptic Ulceration: Causes of and Design for the Second Operation on the Stomach, Lancet **1**:1, 1939.

53. Abbott, W. O., and Rawson, A. J.: A Tube for Use in the Postoperative Care of Gastro-Enterostomy Patients—A Correction, J. A. M. A. **112**:2414 (June 10) 1939.

54. Bartlett, M. K.; Jones, C. M., and Ryan, A. E.: Vitamin C Studies on Surgical Patients, Ann. Surg., to be published.

55. Elman, R. and Weiner, D. O.: Intravenous Alimentation, with Special Reference to Protein (Amino Acid) Metabolism, J. A. M. A. **112**:796 (March 4) 1939.

utilized, as was indicated experimentally and clinically by the nitrogen balance, the regeneration of serum protein and the reduction of nutritional edema. This mixture was administered to about 20 patients, but only 8 received large amounts for more than one or two days. The method is still too expensive for practical purposes, largely on account of the necessity for the addition of tryptophan, which is essential for the support of normal nitrogen metabolism, but the idea is sound, and the necessity for such a procedure will undoubtedly lead to more practical results.

Accurate knowledge of the postoperative appearance and function of the stomach after subtotal resection is still lacking, although roentgenologic and gastroscopic studies are gradually accumulating. The importance of these studies is obvious inasmuch as they undoubtedly help to explain the persistence of many troublesome symptoms after radical operations. One such study is that reported by Shekhter,[56] who made roentgen observations in 60 cases of subtotal resection for ulcer. Eleven cases were studied during the three months after gastric operation, and 10 cases were studied for periods of two, three and five years after operation. Careful observations were made on the inflammatory mucosal edema, with narrowing of the stoma and delay in gastric evacuation, which appeared shortly after resection. This edema disappeared in uncomplicated cases in the course of three months, leading to the type of evacuation characteristic for many given types of resection. The need for correlation of such observations with direct gastroscopic observations is obvious.

Cancer.—Cancer of the stomach of necessity attracts a good deal of attention, but the means of making an early diagnosis of this condition still leave much to be desired. Hurst[57] has contributed an article on cancer of the alimentary tract that is rather interesting, particularly in its analysis of cancer statistics. Various social strata in England are studied and a comparison made with similar strata in Holland. Hurst brings his account of cancer of the stomach up to date and discusses its genesis in a general but interesting fashion. He quotes Cramer to the effect that the total incidence of cancer is approximately the same in all countries, all classes and both sexes but expresses the view that the incidence of cancer of the stomach shows a remarkable difference in different nations and classes. Thus cancer of the stomach accounts for only 22 per cent of deaths from cancer in males in England, compared with 45 per cent in Sweden and 55 per cent in Holland. It is twice as

56. Shekhter, I. A.: Shape, Position and Motor Function of Stomach After Resection for Ulcer, Novy khir. arkhiv **41**:346, 1938.

57. Hurst, A.: Cancer of the Alimentary Tract: Its Pathogenesis and Its Prophylaxis, Lancet **1**:533, 1939.

frequent in the lower social classes in England as among the well-to-do, whereas the incidence of carcinoma of the colon and rectum is the same in both classes. A comparison between the figures obtained from Guy's Hospital and other English general hospitals representing the English poor and those obtained from New Lodge Clinic, representing the well-to-do and from University Clinic of Amsterdam and Utrecht shows that in Holland the stomach is involved in 37 per cent of cases of cancer of the alimentary tract as compared with 63 per cent in England. In agreement with other authors he stresses the apparent importance of the excessive use of alcoholic beverages and tobacco in association with cancer of the esophagus. One important point in regard to cancer of the colon is Hurst's impression that it is not found with any greater frequency in patients suffering from diverticulitis than in the general run of patients.

Another excellent presentation of this subject is that of Jordan,[58] who reports on 251 cases, in 187 of which the carcinoma was considered operable. The age incidence, the localization of the cancer and the relation to achlorhydria are all discussed. She emphasizes the importance of periodic check-ups for patients who have achlorhydria, especially when it is known to be in association with healed gastric ulcer. Instead of accepting the usual defeatist attitude that is held by so many members of the medical profession, she makes a plea for "rugged individualism" in the treatment of cancer of the stomach, with disregard for the average discouraging prognosis of the disease. This attitude is warranted by the fact that in a series of approximately 100 cases in which the patient was followed after resection of a tumor the patient lived four years or more after operation in almost one seventh of the instances.

A point of some clinical interest is that raised by Rivers and Dry [59] in a discussion of pain in relation to cancer of the stomach. In a general way it can be said that patients with cancer of the stomach whose gastric secretion is normal or above are much more likely to experience pain than those who have achlorhydria or only a trivial amount of hydrochloric acid. Such a point is not unexpected but is worthy of mention.

An unusual case report of Phillips and Rivers [60] should be mentioned, in which 2 carcinomas involved the stomach in the same patient, with an eleven year interval between them. The first tumor appeared when the

58. Jordan, S. M.: Medical Aspect of Cancer of the Stomach, J. A. M. A. **112**:618 (Feb. 18) 1939.

59. Rivers, A. B., and Dry, T. J.: Pain in Cancer of Stomach: Preliminary Report, Am. J. Digest. Dis. **5**:732, 1939.

60. Phillips, R. B., and Rivers, A. B.: Two Carcinomas Involving the Same Stomach with an Eleven-Year Interval Between Them, Am. J. Digest. Dis. **6**:37, 1939.

patient was 22 years of age, was extremely malignant but was successfully removed, and the patient survived for eleven years, at which time he was operated on a second time, again for cancer of the stomach. If the second tumor represented a recurrence, the interval of freedom from symptoms is of interest. However, the fact that the histologic appearance of the second growth appeared definitely different from that removed at the first operation makes it probable that the second cancer arose independently of the first one.

A note by Dobbs [61] on the treatment of pyloric stenosis with atropine methylnitrate (eumydrine) may be mentioned. A series of 20 infants with pyloric stenosis were treated with this drug, and 16 were apparently cured. Three were operated on successfully after atropine methylnitrate had failed to relieve vomiting. One infant died during treatment with the drug. The diagnosis of pyloric stenosis was based on a typical history, visible peristalsis and a palpable pyloric tumor. Dobbs points out that dehydration and alkalosis were relieved by the subcutaneous administration of physiologic solution of sodium chloride before the administration of the drug. Hypodermoclyses were used as long as the intake of fluids by mouth was insufficient.

Another article referable to pylorospasm is that of Wolfe,[62] who reports 5 cases in which the condition simulated ruptured or perforated peptic ulcer. Prompted by the similarity between spasm of the digestive tract and bronchial spasm, the author conceived the idea of administering epinephrine as a diagnostic measure. Marked relief of the spasm of pain was observed in five to fifteen minutes in every instance. The author feels that in the presence of perforation epinephrine would have no effect and that therefore its use constitutes a diagnostic method of importance. The procedure is of interest, although one is inclined to believe that a careful physical examination would permit a correct diagnosis in most instances. The procedure is accompanied by no risk, however, and conceivably may be of real diagnostic value.

Gastroscopy.—The latest addition to methods for the diagnosis of disease of the stomach, gastroscopy, has been thoroughly reviewed during the past year. Few, if any, new observations have been added to the large number made by Schindler, Benedict and numerous others. A comprehensive summary of the entire subject has been presented by Schindler,[63] which will be found authoritative by those interested in this extremely important subject.

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61. Dobbs, R. H.: The Treatment of Pyloric Stenosis with Eumydrin, Lancet **1**:12, 1939.

62. Wolfe, J.: Hypodermic Use of Adrenalin for Differential Diagnosis Between Acute Pylorospasm and Ruptured Peptic Ulcer, Virginia M. Monthly **65**:405, 1938.

63. Schindler, R.: Role of Gastroscopy in Recognition and Identification of Gastric Lesions: Collective Review, Internat. Abstr. Surg. **67**:443, 1938.

A technical modification of the flexible Wolfe-Schindler gastroscope has been devised by Jennings.[64] It consists of an instrument with a magnetic control of the objectives. The author claims that it gives a closer view of lesions of the lesser curvature and diminishes blind areas, although it fails to give complete visualization of the antrum. It is used in conjunction with a narrow angle gastroscope. It is questionable whether this modification offers any real advantages over the instrument at present in almost universal use.

Observations on the effect of acetylsalicylic acid and of certain other substances on the stomach are reported by Douthwaite and Lintott.[65] They confirm the general impression that acetylsalicylic acid is a gastric irritant and apparently may produce submucous hemorrhages and chronic gastritis. The calcium salt of acetylsalicylic acid seems to be the least irritating preparation available.

Schindler [66] calls attention to the importance of localized gastric purpura as evidenced by mucosal hemorrhages and round accumulations of pigment, found most frequently about 3 cm. above the angulus along the lesser curvature. These absorb slowly, and the lesion may occasionally develop into a hemorrhagic erosion. He suggests the possibility that such a hemorrhagic lesion may precede the occurrence of the acute stage of gastroduodenal ulceration. He also presents [67] an excellent summary of gastroscopic observations made on 23 patients with pernicious anemia, 3 of whom were examined before and after adequate treatment and 14 of whom were observed only after intensive therapy. All of the untreated patients showed superficial gastritis with atrophy, or patchy or diffuse atrophy. After treatment 4 patients showed no improvement in the gastric mucosa, and an additional patient showed progression of gastric atrophy under adequate therapy. Seven patients who had received proper treatment of the underlying condition showed a normal mucosa of the gastric antrum, while in another there was almost complete regeneration of the gastric mucosa. In 4 patients all portions of the stomach appeared to be absolutely normal. He explains these findings by assuming that in pernicious anemia there are two separate diseases of the stomach; he supposes that primarily there is a dysfunction of the mucosal cells which produce the antianemic factor

64. Jennings, D. B. M.: A Flexible Gastroscope with Magnetic Control of Objective, Lancet **1**:1153, 1939.

65. Douthwaite, A. H., and Lintott, G. A. M.: Gastroscopic Observation of Effect of Aspirin and Certain Other Substances on the Stomach, Lancet **2**:1222, 1938.

66. Schindler, R.: Chronic Localized Gastric Purpura, Am. J. Digest. Dis. **5**:796, 1939.

67. Schindler, R., and Serby, A. M.: Gastroscopic Observations in Pernicious Anemia, Arch. Int. Med. **63**:334 (Feb.) 1939.

and that secondarily there is degeneration of the surface epithelium with superimposed gastritis, which may or may not heal when the deficiency state is eliminated. The secondary inflammation is usually associated with similar disturbances of the tongue and intestine, dysfunction of the hemopoietic apparatus and combined degeneration of the spinal cord. At times, he believes, one may see a severe but reversible atrophic gastritis without associated blood changes, and suggests that a new term be substituted for that of "antianemic factor." The article is more complete than any other previously published on the subject, and it confirms many of the previous findings.

Robertson [68] comments on the findings in cases of ulcerative gastritis in relation to residual lesions. He describes in detail the microscopic appearances of stomachs with healing or incompletely healed lesions and emphasizes the importance of frequency of superficial mucosal hemorrhages, citing Beaumont's original observations. He states that the hemorrhages that are due merely to overdistention of capillary loops are always followed by necrosis and subsequently by more or less healing. From these superficial lesions, deeper and more extensive ulcerations into the muscularis may occur, with distortion of the gastric architecture, and these are similar to the lesions produced experimentally with cinchophen. The residual (unhealed) lesions of "ulcerative gastritis" appear to be the most common lesions of the gastric wall. The author quite correctly objects to the use of the term "chronic gastritis" without modification.

Bank and Renshaw [69] present an interesting attempt to correlate observations of the secretory and motor functions with gastroscopic findings. In 50 patients with chronic superficial gastritis no characteristic secretion was noted. Hyperacidity was found in 50 per cent of the patients and anacidity in 25 per cent, these figures differing from those in other reports which have included all forms of gastritis. The authors claim that the incidence of anacidity is greater in this group of patients than in the group without gastrointestinal symptoms, but unfortunately they do not take into consideration the age distribution. Chronic superficial gastritis, according to Bank and Renshaw, is characterized by a delayed emptying time in more than half of the patients, and patients with achlorhydria and gastritis fail to show hypermotility. Sixty-five additional patients with gastroduodenal ulcerations were studied by means of the gastroscope to estimate the relationship between

68. Robertson, H. E.: Ulcerative Gastritis and Residual Lesions, J. A. M. A. **112**:22 (Jan. 7) 1939.

69. Bank, J., and Renshaw, J. F.: Chronic Superficial Gastritis: Correlation of Gastric Analysis and Clinical Study with Gastroscopic Examination, J. A. M. A. **112**:217 (Jan. 21) 1939.

gastritis and six hour retention as observed in roentgen examination. The conclusion was reached that gastritis is not dependent on retention.

An article by McNeer and Barowsky [70] based on more than 200 gastroscopic examinations of 143 patients contains certain points of importance. The authors show that the belief that true achylia is an expression of atrophy of the gastric mucosa is not supported by gastroscopic study. This, of course, is in agreement with numerous recorded observations on patients with pernicious anemia in remission. One observation, while not original, is important, namely, that gastritis may occasionally simulate a gastric neoplasm to such an extent that even gastroscopically it may be difficult to differentiate between the two. This is particularly true in occasional cases of diffuse scirrhous carcinoma.

SMALL INTESTINE

Aside from a consideration of duodenal ulcer the articles concerning this portion of the alimentary tract deal primarily with pathologic or anatomic abnormalities and for the most part are of only moderate interest. One article on the physiology of the small intestine is that of Althausen and Stockholm.[71] These authors, who have been interested in the absorptive activity of the small bowel for some time, report on the influence of the thyroid gland on absorption in the digestive tract. Administration of a thyroid extract to rats markedly increased the absorption of dextrose, galactose, xylose and oleic acid but did not affect the absorption of alanine. Thyroidectomy caused considerable reduction in the absorption of dextrose, and the absorption of xylose in rats treated with thyroxin was increased, apparently by abnormally rapid emptying of the stomach. The absorption of dextrose, galactose and oleic acid was increased with thyroxin treatment, probably because of a stimulation of the mechanism of phosphorylation. This increased absorption of dextrose appears to take place chiefly in the small intestine. Althausen's findings indicate that the thyroid hormone influences intestinal absorption mainly by increasing phosphorylation and by stimulating gastric emptying. The discovery that thyroxin specifically stimulates the absorption of substances susceptible of phosphorylation and that phlorhizin inhibits this stimulating action confirms Verzár's theory of selective intestinal absorption through phosphorylation. Clinically, altered absorption is an important factor in the production of abnormally high sugar tolerance curves in patients with hyperthyroidism and unusually low sugar tolerance curves in patients with myxedema.

70. McNeer, G., and Barowsky, H.: A Gastroscopic Study of the Incidence of Chronic Gastritis in Common Gastric Afflictions, Am. J. Digest. Dis. **6**:180, 1939.

71. Althausen, T. L., and Stockholm, M.: Influence of the Thyroid Gland on Absorption in the Digestive Tract, Am. J. Physiol. **123**:577, 1938.

A report by Lieber, Stewart and Lund [72] contains a good statistical study of 222 cases of carcinoma of the prepapillary portion of the duodenum, and includes 17 of their own cases. It should be pointed out that inadequate roentgen studies seem to have been made in the vast majority of cases, which may explain the fact that in only 17 per cent of the cases was the condition correctly diagnosed previous to operation. The mortality following operative treatment of the condition is extremely high, representing 50 per cent of the 122 cases that came to surgical attention. There was 78 per cent mortality among 51 patients subjected only to palliative surgical treatment for obstructive jaundice, whereas of 57 patients who had the primary growth resected, only one third died. Jaundice occurred in practically all of these patients, pain in about two thirds and fever in one third. A palpable mass was noted in only 4 patients, although the liver was palpable in three fourths of the patients and the gallbladder in one half.

Foshee and McBride [73] report a case of leiomyosarcoma of the duodenum, obviously a rare condition inasmuch as only 5 other cases are mentioned in the literature. In most of the reported cases the tumor occurred in the third portion of the duodenum. It is of interest that in these cases roentgenograms offered no diagnostic aid, with a single exception. In every case the tumor was very large but did not cause stenosis or dilatation of the bowel. Surgical removal was extremely dangerous because of probable damage to the superior mesenteric artery or its branches with subsequent changes in the bowel. Four of the patients were operated on, and 5 of the 6 patients died of pulmonary embolism or pulmonary thrombosis.

Two cases of diverticulum of the duodenojejunal junction are recorded by Raven [74] and are of interest only because of the rarity of a diverticulum occurring in this position.

Weiss [75] discusses the etiologic factors of megaduodenum and reports on the abnormality as observed in 6 members of the same family during three generations. In 5 of these 6 patients there were associated congenital abnormalities. In discussing the condition he notes that persons in whom it is congenital may remain symptom free for years, and he advises only conservative treatment for those patients who complain

72. Lieber, M. M.; Stewart, H. L., and Lund, H.: Carcinoma of Prepapillary Portion of the Duodenum, Ann. Surg. **109**:383, 1939.

73. Foshee, J. C., and McBride, W. P. L.: Leiomyosarcoma of the Duodenum: Report of a Case and Review of the Literature, J. A. M. A. **112**:2497 (June 17) 1939.

74. Raven, R. W.: Diverticula of the Duodenojejunal Flexure, Lancet **1**:203, 1939.

75. Weiss, W.: Zur Aetiologie des Megaduodenums, Deutsche Ztschr. f. Chir. **251**:317, 1938.

of mild peristaltic disturbances. He expresses the opinion that surgical intervention may be necessary if the symptoms are serious, but quite correctly states that gastroenterostomy, duodenojejunostomy and a Billroth II type of operation with a terminolateral gastroenterostomy all fail to help. He advocates modification of the Billroth II operation as devised by Roux. It is important to point out, however, that the most favorable results reported in relation to surgical treatment in this condition are probably examples of wishful thinking, and surgical measures should be considered only after all other methods have failed to provide reasonable control.

Increased interest in diseases of the small bowel has been obvious during recent years. With improved methods of roentgenologic examination, possibly with intubation of the small bowel and with closer attention to the exact reference of the pain experienced in these conditions, there is no doubt that more accurate diagnoses are possible than previously. Lesions such as those reported by Shaw can frequently be localized, even though their exact nature cannot be definitely diagnosed. Reference is made to his article merely because of the importance of considering the somewhat unusual but not too infrequent lesions of the small bowel. Shaw [76] reports 5 cases of polyposis of the small intestine, a relatively rare clinical entity but of importance because of the tendency toward malignant degeneration. Preoperative diagnosis is difficult, largely because early signs and symptoms are insufficient to cause patients to consult a physician. Frequently such lesions are first brought to the attention of the surgeon because of an abdominal crisis caused by intestinal obstruction from intussusception. It is worthy of remark that patients suffering from these and similar lesions frequently complain to a doctor of umbilical distress, which in itself is a symptom that should always call attention to the possibility of disease of the small intestine.

Ileitis continues to be the subject of numerous articles, but little has been added to knowledge of the disease except as to its clinical manifestations. An unusual report is that of Brown and Scheifly,[77] who present data on 3 siblings, 2 sisters and a brother, who exhibited various manifestations characteristic of regional enteritis. A second brother was known to have intestinal disturbances presenting many similar features, but permission to examine his colon and ileum have not been obtained. The report is of interest inasmuch as it is extremely rare for either colitis or enteritis to occur in more than one member of a family. In commenting on the treatment of the disease the authors

76. Shaw, E. A.: Polyposis of the Small Intestine: Report of Five Cases, New England J. Med. **220**:236, 1939.

77. Brown, P. W., and Scheifly, C. H.: Chronic Regional Enteritis Occurring in Three Siblings, Am. J. Digest. Dis. **6**:257, 1939.

consider that resection of the diseased portion of the bowel is the therapeutic procedure of choice at present but express the hope that a better understanding of this unusual condition may in the future offer a less radical treatment.

This conservative point of view as regards therapy of regional enteritis is one that is occasionally voiced, and reports similar to that of Kross [78] must not be overlooked. He reports the results in 3 cases in which the bowel was operated on to an extent which would usually be considered inadequate. In the first patient only the appendix was removed and the diseased bowel was left undisturbed; a second patient had only an enterostomy; and the third, a "side-tracking" colostomy. These patients had no recurrences during periods of five and a half, four and three-quarters and one and a quarter years, respectively. Although numerous instances can be obtained of fairly or very satisfactory responses to conservative medical management of the condition, it is obvious that in the present state of knowledge surgical operation must constitute an important form of therapy.

Because of suggestive clinical and experimental evidence that the disease may originate in the mesenteric lymphatics, Mixter and Starr [79] believe that the successful results following resection of the affected ileum depend primarily on wide excision of the involved mesentery and its lymph nodes. They also believe that failure to carry out this type of treatment may bear a definite relation to the recurrences frequently observed after surgical treatment.

The question of the amount of small bowel that can be safely resected is particularly pertinent to the subject of ileitis. Various studies have appeared from time to time on food absorption in patients who have had portions of the bowel removed. West and co-workers [80] present such studies on digestion and absorption in a man with 3 feet (90 cm.) of small intestine. This patient had five resections of the small bowel over a period of eleven years, with less than a foot (30 cm.) of jejunum remaining. At exploration, several months prior to metabolic studies, the remaining small bowel was found to be dilated and hypertrophied almost to the size of the normal large intestine. It was found that under the existing conditions about 25 per cent of the ingested protein and 45 per cent of the fat were lost in the feces, representing approximately 25 per cent of the calorific value of ingested food. Practically all of the carbohydrate in the diet was absorbed

78. Kross, I.: Terminal Ileitis: Conservative Surgical Treatment, Am. J. Digest. Dis. **5**:313, 1938.

79. Mixter, C. G., and Starr, A.: Further Experience with Regional Enteritis, New England J. Med. **219**:37, 1938.

80. West, E. S.: Montague, J. R., and Judy, F. R.: Digestion and Absorption in Man with Three Feet of Small Intestine, Am. J. Digest. Dis. **5**:690, 1938.

and utilized. A high calcium and viosterol intake was necessary in order to keep the man in a positive calcium balance, and, with what was apparently only about one sixth of the small bowel remaining, a fairly satisfactory existence was possible. Fat absorption would appear to be the chief limiting factor necessitating anything like the normal length of small bowel. The regulation of diet in this case may well be utilized as a guide to the dietary treatment of patients with similar conditions.

The causes of ileus of the small intestine are well known. Two recent reports are of some interest in this connection. Adamson and Hild[81] report the development of complete obstruction of the ileum in an infant within thirty-six hours after birth. The obstruction was primarily due to a packing of the lower 18 inches (45.5 cm.) of the ileum with inspissated waxy meconium and associated intussusception below the mass. Twenty-two other cases are reported in the literature, although the condition must be considered as a rarity.

Another unusual report is that of Badertscher,[82] who describes a triple intussusception of the ileum in a child as a result of an automobile injury. This case report is only the fourth in the literature of traumatic intussusception, although numerous cases of multiple intussusception in children have been described. Laparotomy showed the ileum to be intussuscepted in three places. Reduction was possible, with complete recovery.

The diagnosis of partial or complete intestinal obstruction is still a problem to be solved largely on the basis of clinical experience. It is true, however, that many physicians are still unaware of the diagnostic help that can be obtained from the roentgenologist once the condition is suspected. Although there is little, if anything, new in the article on roentgen diagnosis of complete and partial intestinal obstruction by Solis-Cohen and Levine,[83] the importance of this diagnostic procedure is properly emphasized. They stress the extreme diagnostic importance of flat or survey roentgenograms of the abdomen in the early stages of acute intestinal obstruction and the need for examining patients in the prone, supine and upright positions. With other roentgenologists, they agree that the absence of a stepladder appearance does not rule out ileus and indicate that they consider the appearance of trapped gas and hairpin turns as among the earliest signs of acute intestinal obstruction. Excellent illustrations accompany the article.

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81. Adamson, E. W., and Hild, J. R.: Meconium Ileus, J. A. M. A. **112**:2275 (June 3) 1939.

82. Badertscher, V. A.: Traumatic Triple Intussusception of the Ileum in a Child, J. A. M. A. **112**:422 (Feb. 4) 1939.

83. Solis-Cohen, L., and Levine, S.: X-Ray Diagnosis of Complete and Partial Acute Intestinal Obstruction, Radiology **31**:8, 1939.

Another detailed discussion of roentgen signs to be observed in this condition is presented by Høyer,[84] who gives a particularly full description of the roentgen signs to be noted in the first twenty-four hours of obstruction of the small bowel, before the development of diagnostic clinical signs and symptoms. He reviews the details of Kloiber's original studies of 100 cases and illustrates the findings to be made by roentgenologic examination without contrast mediums in his own 46 cases. He stresses the importance of fluoroscopic examination for noting changes in the fluid levels as an important differential point between mechanical and paralytic ileus. Among other important diagnostic points he mentions the more or less complete absence of gas from the large bowel in the presence of an obstruction of the small bowel.

The treatment of intestinal obstruction by intubation is again considered by Abbott.[85] The technic for intubation of an obstructed bowel, he has previously described. Observations on 27 patients are presented, and the entire article, including a discussion of the condition, is extremely sound and clinically important. The data, together with the enclosed diagrams and roentgenograms, are convincing. The author points out that passage of a tube to the point of obstruction is of particular value because it converts a situation calling for emergency measures into one in which the time of operation, if this is performed at all, becomes a matter of election. He recognizes that the great contraindication to intubation is gangrene and that success with the procedure therefore demands excellent clinical judgment. Failure to relieve symptoms as the intubation proceeds should be the indication for a decision to operate. If, on the other hand, pain and vomiting abate following intubation, and there is disappearance of distention, time is gained for further study and for insuring proper nourishment of the patient. Abbott concludes from his observations:

> Intubation not only rarely adds to the hazards of acute intestinal obstruction, but frequently improves the condition of the patient, increases his comfort, enables the physician to determine the character of the obstructing lesion, simplifies its resection when that proves necessary, safeguards convalescence, and above all contributes to safety by converting an emergency condition into one completely under the physician's control.

The prevention of paralytic ileus following operation is discussed in an interesting article by Cairney,[86] who does not include ileus due to

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84. Høyer, A.: X-Ray Diagnosis of Intestinal Obstruction, Acta radiol. **19**: 409, 1938.

85. Abbott, W. O.: Intubation of the Human Small Intestine: The Treatment of Intestinal Obstruction and a Procedure for Identifying the Lesion, Arch. Int. Med. **63**:453 (March) 1939.

86. Cairney, J.: Prevention of Paralytic Ileus, New Zealand M. J. **37**:334, 1938

peritonitis. Although the article describes no new measures, the author summarizes therapeutic procedures in a logical manner and one worthy of presentation. Morphine is administered if needed during the first forty-eight hours after operation. On the third morning Cairney examines the abdomen with a stethoscope for evidences of peristalsis. If this is present, an enema is given, and if good results are obtained, the enema is followed by an aperient. If peristalsis is absent and distention is commencing, prostigmine and acetylcholine are administered, followed by an enema. Morphine is given only at night, for crampy pain. If no peristalsis and no distention are present, one has the choice of employing an enema or first using prostigmine and acetylcholine. Cairney warns against using an aperient until satisfactory results have been obtained by an enema.

Demidova [87] in one of several articles published in a symposium on acute ileus describes changes in the blood picture in this condition and in incarcerated hernia. In 100 cases of incarcerated hernia there was a moderate increase in the number of red cells and the percentage of hemoglobin before the possible appearance of dehydration. The author thinks that these changes were due to stimulation of the vegetative nervous system with an outflow of red blood cells from reserve depots. These changes are accompanied by mild leukocytosis. In 158 cases of acute intestinal obstruction an elevation of the red blood cell count was noted up to 6,000,000, of the hemoglobin up to 120 per cent and of the white blood cell count up to from 12,000 to 30,000, with a distinct shift of neutrophils to the left. In the cases of ileus of the small bowel the increases in the number of red cells, hemoglobin and white cells were never more marked than the corresponding increases observed in an equal number of cases of obstruction of the sigmoid. The author concludes that the blood picture reflects three stages of obstruction: (1) a slight initial increase of red cells, hemoglobin and white cells, due to initial pain and irritation with stimulation of the vegetative nervous system; (2) a subsequent rise, which he attributes to intoxication, dehydration and an increase in the viscosity of the blood; (3) with beginning infection, peritonitis and further intoxication and subsequent leukopenia.

Another well worn subject that of late has deservedly attracted a great deal of attention is appendicitis. In spite of innumerable articles on the subject, mortality from this cause remains at an appallingly high figure, and it is to be noted with regret that, if anything, there is a higher mortality from appendicitis among physicians than among the laity. Among numerous articles, a few have been chosen. Kelly

87. Demidova, P. N.: Blood Picture in Acute Ileus, Vestnik khir. **56**:356, 1939.

and Watkins [88] present an interesting review of the results in 1,000 consecutive cases of acute, simple and chronic appendicitis in which operations were performed within recent years and contrast the results with those obtained in 1,000 similar cases reported by the same authors in 1931. The results in the series under discussion show no great variation from those previously reported except for a sharp increase in the death rate noted for those classified as instances of the acute suppurative type of appendicitis. This increase rose from 9 per cent in the first series of cases to a mortality of 23 per cent in the group under discussion. The authors believe that this rather alarming increase in mortality is due to a delay in operating because of economic changes during the depression years and a tendency to use home remedies, including purgatives, as well as to factors complicating diagnosis. The same increase in the number of deaths from acute appendicitis is noted in an entirely similar report made by Quain and Waldschmidt on two 1,000 case studies reported in 1928 and 1934, respectively. These authors reported a mortality of 18.8 per cent during the depression years, as compared with a mortality of 10 per cent prior to that time.

The question of deferring operation in the presence of peritonitis due to rupture of an acutely inflamed appendix in a child is discussed by Elman.[89] The decision to postpone operation, he thinks, depends not so much on the presence or absence or degree of peritonitis as on the general condition of the child. In a group of 181 children operated on for peritonitis following rupture of an acutely diseased appendix the total mortality was 15.5 per cent. Thirty-three were classified as extremely toxic, and, of the remaining patients, only 9 succumbed, making a mortality of 6 per cent in the nontoxic group. The mortality was 70 per cent in those operated on at once and only 30 per cent in those operated on after a delay of from nine to twenty-four hours; whereas in the nontoxic group the condition was reversed, a delay in operation causing a 15 per cent mortality as opposed to a mortality of only 3.5 per cent in those children operated on immediately. These figures seem extremely high in the face of another report by Bruce,[90] who operated on 467 children suffering from acute appendicitis, with a total mortality of only 1.9 per cent, until one realizes that Elman's patients were selected from a group whose appendixes had ruptured.

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88. Kelly, F. R., and Watkins, R. M.: Appendicitis in Adults: Review of Two Thousand Consecutive Cases, with Comments on the Rising Mortality of the Acute Suppurative Type, J. A. M. A. **112**:1785 (May 6) 1939.

89. Elman, R.: Peritonitis Due to Ruptured Acute Appendicitis in Children: Influence of Delay in the Operative Mortality, Am. J. Digest. Dis. **5**:804, 1939.

90. Bruce, G. G.: Diagnosis and Treatment of Acute Appendicitis in Children, Lancet **1**:1247, 1939.

Love [91] considers that in those cases of appendicitis in which there is a palpable mass this is due either to abscess or to local peritonitis. In discussing the danger of immediate operation he reports an average mortality of 6 per cent or more, as opposed to an average mortality of under 3 per cent in cases in which he used expectant medical treatment. He is careful to point out that expectant treatment is not particularly suitable for children and old people.

The numerical importance of appendicitis among college students has received much attention in recent years, and an illuminating article is that of Schmidt and Joachim,[92] who reported on 1,303 students with appendicitis encountered at the University of Wisconsin.

The question of the treatment of the chronically disturbed appendix continues to receive consideration, but little, if anything, new or important has been presented. An undoubtedly correct point of view is that of Swalm and Morrison,[93] who plead for a conservative attitude toward appendectomy for "chronic appendicitis." They stress particularly the infrequency with which this condition is correctly diagnosed in the presence of the syndrome of a spastic, irritable or unstable colon.

Reference should also be made to a thoughtful study by Shelley [94] of 881 cases of "chronic appendicitis." Shelley believes that he has adequate evidence that such a clinical entity exists, but he emphasizes the extreme importance that should be paid to a definite localization of physical findings and to the nature and frequency of attacks. Although presenting an obviously surgical point of view, the author is extremely careful to insist on the utmost diagnostic care in ruling out other conditions simulating appendicitis. The article is well worthy of careful perusal.

Intestinal tuberculosis still presents difficulties in diagnosis and treatment. Tsigelnik [95] discusses in some detail 150 cases of this condition and points out one important factor, namely, that symptoms were entirely absent in 6 of 50 persons who came to autopsy with this diagnosis and for whom the diagnosis was confirmed. Of the 150 cases, roentgen study following a barium sulfate meal and enema gave positive results in 80 per cent; occult blood was noted in the stools in 18 per cent, and hypochromic anemia (hemoglobin under 60 per cent) was

91. Love, R. J. M.: The Appendix Mass, Lancet **1**:1252, 1939.

92. Schmidt, E. R., and Joachim, F. G.: The Student Health Problem of Appendicitis: Report of 1,303 Cases at Student Infirmary and Wisconsin General Hospital, Journal-Lancet **58**:329, 1938.

93. Swalm, W. A., and Morrison, L. M.: Plea for Conservatism in Appendectomy for Chronic Appendicitis: Observations on the Spastic, Irritable or Unstable Colon Syndrome, Pennsylvania M. J. **41**:988, 1938.

94. Shelley, H. J.: Chronic Appendicitis: Is It a Clinical Entity? Arch. Surg. **37**:17 (July) 1938.

95. Tsigelnik, A. Y.: Intestinal Tuberculosis, Sovet. vrach zhur. **43**:977, 1939.

noted in 80 per cent. Of 50 cases in which treatment was by pneumoperitoneum, the author reports that remission for a period of twelve months or more was obtained in 32. Like other writers, he stresses the importance of an attempt at prophylaxis of intestinal tuberculosis through correction of habitual constipation, instructions not to swallow any sputum and collapse therapy to render the sputum bacillus free.

In a rather poorly written article on the same subject Hardt and his collaborators [96] report some observations of interest on the treatment of intestinal tuberculosis in 238 cases. Favorable results are attributed by the authors in part to the administration of calcium gluconate by mouth, intravenously or intramuscularly. Ultraviolet radiation is thought to have aided the favorable results obtained by the use of calcium. As in the preceding article, collapse therapy is mentioned as an important factor in the treatment of gastrointestinal tuberculosis, probably through improvement in the pulmonary condition and a resulting decrease in the number of bacilli in the sputum. These authors also emphasize the necessity of consistent and careful expectoration as a prophylactic measure. It seems possible that the advantages of calcium therapy are somewhat overemphasized by these workers inasmuch as of 163 patients showing improvement in gastrointestinal symptoms, 134 had received collapse therapy.

A review of the therapeutic aspects of the treatment of intestinal tuberculosis is presented by Mayer and Dworkin,[97] who point out the excellent results frequently obtained by the cautious use of roentgen and the enthusiastic use of ultraviolet therapy.

Charr and Cohen [98] have determined the incidence of intestinal tuberculosis in necropsy studies of patients who died of tuberculous anthracosilicosis and patients who died of pulmonary tuberculosis without anthracotic involvement. The incidence of intestinal tuberculosis was approximately 50 per cent in the subjects without anthracosis, whereas it occurred in only 20 per cent of patients showing anthracosis as well as pulmonary tuberculosis.

An interesting clinical report on disease of the small bowel is found in an article by Wolpaw,[99] in which he describes 3 cases of ulcerative hyperplastic tuberculosis of the small intestine. Although this is occasionally a cause of intestinal obstruction, its rarity, together with the fact

96. Hardt, L. L.; Weissman, M.; Coulter, J. S., and Henrichsen, K. J.: Treatment of Gastrointestinal Tuberculosis, J. A. M. A. **112**:691 (Feb. 25) 1939.

97. Mayer, E., and Dworkin, M.: Roentgen and Light Therapy of Intestinal and Peritoneal Tuberculosis, Radiology **31**:35, 1938.

98. Charr, R., and Cohen, A. C.: Tuberculosis of Intestines in Tubercular Anthracosilicosis, Am. J. M. Sc. **196**:83, 1938.

99. Wolpaw, S. E.: Isolated Hyperplastic Ulcerative Tuberculosis of the Small Intestine, Am. Rev. Tuberc. **38**:32, 1938.

that as a rule it is unaccompanied by evidence of active pulmonary disease, makes the report of importance. This is particularly so because a reasonably early diagnosis of the condition may frequently be followed by successful surgical removal of the local lesion.

LARGE INTESTINE

The physiology of the large intestine has been studied by Jackman and Bargen,[100] who introduced a balloon into the human colon through a colostomy opening and observed the effect of various drugs commonly used to lessen the tone of the musculature of the bowel. Of the spasmolytic drugs employed, glyceryl trinitrate and amyl nitrite were found to be the most consistently efficacious in decreasing the motility of the large bowel. The increase in tone following the use of morphine, as noted by other investigators, was again demonstrated, and it appeared that benzedrine sulfate did not result in any great decrease in bowel tone. Syntropan (a phosphate of 3-diethylamino-2,2-dimethylpropylester of tropic acid) and trasentin (a synthetic ester of diphenylacetic acid and diethylaminoethanol), synthetic chemical substances resembling atropine, appeared to be as effective antispasmodics as atropine, without the undesirable toxic effects of the latter. It is to be noted, however, that benzedrine, syntropan and trasentin were administered intramuscularly, a method of administration that is not ordinarily employed therapeutically. There is still a real question as to the therapeutic efficiency of these newer synthetic preparations when administered by mouth. The fact that they are more expensive and possibly no better than simple atropine derivatives should be remembered in recommending their use.

The same authors[101] carried out further studies on the influence of papaverine on the muscular tone of the intestinal tract. Papaverine hydrochloride alone or combined with pantopon (a mixture of the hydrochlorides of the opium alkaloids) has seemed to be of value in relieving the abdominal cramps and frequent purulent bloody discharges in colitis. The evidence obtained experimentally by Bargen and Jackman substantiated the antispasmodic effect of the papaverine compound. It appears that it has certain advantages over morphine sulfate in cases in which one desires to immobilize the intestine or put it at rest.

The findings of Beyer and Meek[17] in a study on the effect of benzedrine sulfate on intestinal activity are in agreement with those of other investigators. Only by using excised intestinal strips and high concentrations of the drug could they demonstrate any effect on the intestine.

100. Jackman, R. J., and Bargen, J. A.: Influence of Certain Antispasmodic Drugs on Intestine of Man, Surg., Gynec. & Obst. **67**:63, 1938.

101. Bargen, J. A., and Jackman, R. J.: Influence of Papaverine on Muscular Tone of the Intestinal Tract, Surg., Gynec. and Obst. **68**:749, 1939.

Further studies on the effect of certain parenterally administered drugs on the colon of the dog were carried out by Wolff.[102] A series of experiments were performed on trained unanesthetized dogs having Thiry or Wella colonic fistulas, in order to determine the effect of a number of drugs on the motility of the colon. The drugs were administered parenterally, and recordings were obtained by means of rubber balloons with a kymographic recording apparatus. It was found that calcium salts, physostigmine, hypertonic salt solution and acetylcholine produce increased tone and increased motility. Solution of posterior pituitary U. S. P., pitocin, pitressin, ephedrine, histamine and epinephrine cause decreased tone and decreased motility. Pitocin produces the most striking depressive effect. Hypertonic solution of dextrose and parathyroid extract have little or no effect on colonic motility. Physostigmine and ephedrine used together produce marked stimulation of colonic motility as do also physostigmine and acetylcholine administered simultaneously.

The effect of karaya gum on colonic activity was studied clinically by Ivy and Isaacs[103] in a group of 23 patients. The authors studied the action of the gum, a hygroscopic substance which absorbs water and expands considerably, and noted that it absorbs and holds a large quantity of water and causes only a negligible amount of fermentation. It is not appreciably disintegrated in the alimentary tract and does not appreciably affect digestion of starch or inhibit utilization of vitamin A. It does tend to increase fecal excretion of nitrogen to some extent, and in animals as well as in human beings it causes an increased number of defecations, increases the bulk and moisture of the stools and does not cause any detectable irritation. It relieved constipation in about 80 per cent of the persons in whose treatment it was used. Ivy and Isaacs conclude that it produces no harmful effects and is not habit-forming and that it may prove a valuable addition to the treatment of patients with intestinal difficulties.

An unusual study on the physiology of the alimentary tract is that reported by Maddock and Heath[104] on the excretion of iron from the digestive tract. A histologic study of the entire digestive tract of the dog and of an explant of the colon before and after administration of iron revealed no evidence that iron can be observed in the process

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102. Wolff, L. H.: The Effect of Certain Parenterally Administered Drugs on the Colon of the Dog, Am. J. Digest. Dis. **6**:243, 1939.

103. Ivy, A. C., and Isaacs, B. L.: Karaya Gum as a Mechanical Laxative: An Experimental Study on Animals and Man, Am. J. Digest. Dis. **5**:315, 1938.

104. Maddock, S., and Heath, C. W.: Is Iron Excreted by the Gastrointestinal Tract of the Dog? A Histologic Study, Arch. Int. Med. **63**:584 (March) 1939.

of excretion. Traces of iron seen in the walls of the stomach and large bowel were considered to be in a state of storage rather than of excretion.

Ulcerative colitis, as usual, has received a large amount of attention, and it is becoming apparent that the nature and history of the disease is more clearly understood at the present time than in recent years. It seems fair to state that the causes of the condition are still unknown, although various workers have attempted to find a causative organism. There is almost complete agreement that the diplostreptococcus group of Bargen is probably a secondary invader, and attempts to prove that Bacillus dysenteriae is the usual responsible agent are still far from convincing. An excellent symposium on the entire subject has been presented by Mackie,[105] Jones[106] and Willard and associates.[107] In these three articles the question of therapy is fairly completely covered from both medical and surgical points of view. A perusal of the discussion in this symposium should be of real value to those interested in this disease, a malady which presents one of the most difficult problems of the day. The conclusions in Mackie's paper may well be quoted:

1. Chronic ulcerative colitis appears to be the complex expression of the interaction of several different factors.

2. The disease exhibits an inherent tendency to progression and relapse.

3. Although the prognosis under medical management is good in the pathologically mild and moderately advanced case, the term "apparently arrested" should be substituted for "cured."

4. Prolonged joint medical and surgical observation is essential for the pathologically advanced case.

5. Combined medical and radical surgical treatment offers the best prognosis for many of the pathologically advanced cases.

Jones comments on the extremely bad prognosis of the so-called fulminating form of the disease, a type that usually can be recognized by the curious velvety, diffusely oozing appearance of the rectum and rectosigmoid at sigmoidoscopic examination. Such a condition, as a rule, responds badly to either medical or surgical measures. Among other important points noted in the discussion by Willard and collaborators is the fact that the extent of involvement as shown in roentgenograms does not constitute a reliable prognostic sign. Mackie and the other writers point out the absolute necessity for a close correlation

105. Mackie, T. T.: Medical Management of Chronic Ulcerative Colitis, J. A. M. A. **111**:2071 (Dec. 3) 1938.

106. Jones T. E.: Surgical Treatment of Ulcerative Colitis, J. A. M. A. **111**:2076 (Dec. 3) 1938.

107. Willard, J. H.; Pessel, J. F.; Hundley, J. W., and Bockus, H. L.: Prognosis of Ulcerative Colitis, J. A. M. A. **111**:2078 (Dec. 3) 1938.

between medical and surgical management in dealing with these patients, who present all the extreme manifestations of deficiency disease and chronic infection.

Among various articles contributing to a better understanding of the disease, attention should be directed to that of Paulson,[108] who discusses the confusion frequently existing in the consideration of rectal lesions due to lymphogranuloma venereum and idiopathic ulcerative colitis or other rectal lesions associated with stricture. Paulson discusses experimental and clinical evidence which supports the view that the virus of lymphogranuloma venereum found in intestinal discharge (bowel antigen) or tissue (bowel tissue antigen) is of pathogenic significance. When the bowel antigen reaction is positive it indicates that the virus of lymphogranuloma venereum is in the bowel tissue or the discharge from which it is obtained. He claims that the only direct clinical method now available to determine the presence of the virus in such sources is in the use of bowel antigen. Bowel antigen is important, because the clinical picture is not pathognomonic, and the so-called lymphogranuloma venereum is not always caused by the virus of this disease. In some cases a condition clinically indistinguishable from nonspecific ulcerative proctitis and colitis is found in association with the virus of lymphogranuloma venereum by means of bowel antigen. The pathologic picture grossly and histologically is not pathognomonic, and the use of bowel antigen may aid in the differential diagnosis. The use of Frei antigen alone in difficult cases is not adequate, because the patient may give no reaction to the Frei antigen, whereas bowel antigen may indicate the presence of the virus (anergy). A positive Frei reaction may be produced by an antedated or healed virus infection or by one completely unrelated to the existing bowel disturbance. Paulson's observations are of more than speculative interest and may help to differentiate another small but important group of cases of so-called idiopathic ulcerative colitis.

One of the most important contributions to an understanding of the subject is found in the brilliant observations of Lium.[109] Using a method of colonic explantation, Lium was able to demonstrate in dogs, by direct visualization of the colonic mucosa, that the explants reacted to various stimuli by spasm of the colonic musculature. Whether produced by mechanical stimulation, parasympatheticomimetic drugs or dysentery toxin, this spasm resulted in damage to the overlying epithe-

108. Paulson, M.: Bowel Antigen: Clinical Use of a New Method to Determine the Presence of Virus of Lymphogranuloma Venereum in the Differential Diagnosis of Intestinal Involvements, J. A. M. A. **112**:1788 (May 6) 1939.

109. Lium, R.: Etiology of Ulcerative Colitis: Effect of Induced Muscular Spasm on Colonic Explants in Dogs, with Comment on Relation of Muscular Spasm to Ulcerative Colitis, Arch. Int. Med. **63**:210 (Feb.) 1939.

lial structure, with resultant hemorrhage and ulceration. The mode of action of dysentery toxin in producing ulcerations of the mucosa is thus apparently through the injurious effects of smooth muscle spasm. In association with muscular contractions of the explant the secretion of mucus is immediately increased. When muscular hyperactivity continues, only thin, watery material, inadequate for protective purposes, is secreted. Ulcerated areas are not covered with a coating of mucus until they have healed, thus being exposed to trauma from the passing current. Even after returning to a normal gross appearance, the regenerating epithelium is more sensitive to trauma than the normal epithelium of a colonic graft. Lium discusses the possibility that ulcerative colitis may be conceived as a specific reaction to a number of influences which can initiate spasm of the colonic musculature. These include possible hyperactivity of the parasympathetic nervous system, infections such as bacillary dysentery and vitamin deficiency. Once the colon becomes spastic, it is an organ that can produce damage to its own surface structures. Exhaustion of the secretion of mucus, together with nutritional deficiency, may contribute to the prevention of healing. That muscular spasm may be responsible for lesions of the mucosa of other portions of the gastrointestinal tract is suggested by certain of the experiments under discussion, as well as by a reinterpretation of the work of others.

Lium and Porter [110] contribute an important analysis of 6 fatal cases of ulcerative colitis. Stool cultures and agglutinations for dysentery were negative in 5 of the 6 cases. Of the observations at necropsy that were considered to be of importance, the chief was the distribution of the lesions. At the junction of the rectum and sigmoid the ulcerations developed in three rows running longitudinally. In places the ulcerations extended between the longitudinal rows of ulcers and seemed to follow a linear pattern, which was found to lie directly over the tenial bands. In addition to the usual histologic features, special attention was directed to the absence or marked diminution of mucus in the epithelial cells in early lesions, observed in all sections. The arrangement of the most severe lesions in ulcerative colitis is such that they lie directly over the most powerful muscles in the colon, and the authors suggest that there may be a distinct relationship between the muscles and the lesions. The early stage of ulcerative colitis can be simulated experimentally in animals by hypermotility and spasm of the colonic muscles, features that are prominent in the disease. The authors conclude: "It seems highly probable that ulcerative colitis is primarily

110. Lium, R., and Porter, J. E.: Observations on the Etiology of Ulcerative Colitis: III. Distribution of Lesions and Its Possible Significance, Am. J. Path. 15:73, 1939.

a disease caused by intense muscular spasm and hypermotility, and that therefore the distribution of the lesions follows a muscular pattern. Whatever infectious element is present may well be due to secondary involvement of damaged areas caused by muscular overactivity." It is not difficult to draw an inference from a comparison between these striking observations of Lium and Porter and the many cases in which ulcerative colitis appears to have its origin in an unstable and overstimulated autonomic nervous system. The changes visualized by Lium following the action of parasympathetic drugs are not dissimilar to those reported by White and Jones and bear a direct relationship to the clinical observations of Sullivan, Murray and others.

Further clinical confirmation of the importance of considering individual reactions in relation to ulcerative colitis is contributed by Wittkower,[111] who presents a psychologic analysis of 40 patients with ulcerative colitis. In 37 of these, psychologic abnormalities and disorders were present that were far beyond the range of individual differences observed in the average population, and were found to antedate the initial symptoms of the colitis. Of these 37 patients, 17 had obsessions, 12 had gross hysteria, and 6 were classified as persons of schizoid or depressive mentality. There were no universally common precipitating conflicts, but the authors suggest that the psychologic factor seems to be the most constant cause in this disease, although admitting that the etiologic problem is far from being solved. They conclude that observation of patients with ulcerative colitis appears to justify an attempt at psychotherapy for selected ones with early forms of this disease, a conclusion that is in accordance with the opinion of others. It should be pointed out, however, that psychotherapy should be instituted with extreme caution inasmuch as there is real danger that during the course of treatment the symptoms of colitis may be aggravated to a dangerous degree.

Specific measures for the medical treatment of this disease continue to accumulate in much the same way that ulcer therapy has progressed in recent years. Cheney,[112] following the suggestion that deficiency plays an important role in ulcerative colitis, reports on 8 patients treated by large injections of concentrated liver extract and thiamin chloride. In the majority of these, other methods of treatment had failed to be of benefit, and in all satisfactory remissions were obtained, with clinical and sigmoidoscopic improvement. Although there can be little doubt that satisfactory remissions accompanied the administration of liver

111. Wittkower, E.: Ulcerative Colitis: Personality Studies, Brit. M. J. **2**:1356, 1938.

112. Cheney, G.: Injections of Highly Concentrated Liver Extract in Treatment of Idiopathic Ulcerative Colitis, Arch. Int. Med. **63**:813 (May) 1939.

extract, to which the author gives credit, it is important to remember that similar remissions occur spontaneously and frequently in this disease. It should be pointed out that, although credit is given to liver extract, in reality the treatment included the administration of large amounts of vitamin B_1 in addition to the use of the medical measures that are commonly employed. Cheney's conclusions are at best speculative, and while no means of procuring improvement in this dangerous disease should be overlooked, one feels that the interpretation of his results should be more guarded.

Another report of therapeutic interest is that of Gainsborough,[113] who treated 6 patients by cod liver oil retention enemas. The author frankly states that the method was not certainly curative, but he believes that it was efficacious in shortening the illness in some patients and in reducing pain. He points out that these patients were more tolerant to cod liver oil enemas than to other local applications, a statement that causes one to question whether as a therapeutic measure the method is not merely palliative, although as such it should be regarded as a possible valuable adjunct to therapy.

The degree of deficiency that may occur during the course of ulcerative colitis is reemphasized by Lerner and Rapaport,[114] who describe the results of biophotometric studies in 30 persons suffering from this disease. Approximately one third of the patients showed evidence of inability to adapt normally in the dark, a larger percentage than is found in any general hospital group. The conclusion seems justified that avitaminosis A constitutes one of the complications encountered in this disease and emphasizes the necessity for intensive vitamin therapy.

Although the use of pectin has, for several years, been advocated as an important therapeutic measure in the treatment of ulcerative colitis, the experience of most clinicians has not been particularly favorable. Recent articles, however, by Block and associates[115] and by Arnold[116] suggest the possible therapeutic value of nickel pectinate as a therapeutic measure worthy of trial. Block and associates present a comparative study of the effects of pure pectin and nickel pectinate administered to 95 patients with bacillary dysentery. Pure pectin was found to be ineffective, but definite improvement was observed in every

113. Gainsborough, H.: Treatment of Ulcerative Colitis by Cod Liver Oil Retention Enemata, Lancet **1**:1319, 1939.

114. Lerner, H. H., and Rapaport, H. G.: Biophotometric Studies in Thirty Cases of Chronic Ulcerative Colitis, Am. J. Digest. Dis. **6**:239, 1939.

115. Block, L. H.; Tarnowski, A., and Green, B. H.: Pectin and Nickel Pectinate in Acute and Chronic Bacillary Dysentery, Am. J. Digest. Dis. **6**: 96, 1939.

116. Arnold, L.: Influence of the Ingestion of Nickel Pectinate upon Growth of Young Rats, Am. J. Digest. Dis. **6**:103, 1939.

patient following the use of nickel pectinate. Improvement was apparent in the appearance and general condition of the patients and was accompanied by the disappearance of acute symptoms, tenesmus and bloody diarrhea and by an increase in weight. There seemed to be no contraindications to its use, and no allergic or untoward reactions were observed following the administration of the drug. Arnold, in animal experiments, confirmed the finding of lack of toxicity in nickel pectinate administered in large doses to young rats. There was no interruption of the growth over an eight week period of observation, and no pathologic changes were demonstrable. He further apparently shows by in vitro experiments [117] that many of the metal pectinates possess definite bactericidal activity, although pure pectin seems to show none. Of the preparations studied, silver pectinate possesses the greatest bactericidal activity of any, but nickel pectinate also shows some. It is of some interest that different metal pectinates apparently have individual bactericidal powers that vary with different organisms, such as Bacillus typhosus and Bacillus coli.

It was to be expected that sulfanilamide and sulfanilamide derivatives would be tried in the treatment of such a chronic and dangerous disease as ulcerative colitis. Although it is altogether too early to draw conclusions on the efficacy of such therapy, at least from published data, the article by Bannick and associates [118] is of interest. In a preliminary report they suggest the use of neoprontosil (disodium 4-sulfonamidophenyl-2′-azo-7′-acetylamino-1′hydroxynaphthalene-3′, 6′ disulfonate) and suggest that the prompt subsidence following the use of the drug in milder conditions was due to this particular medication. They recognize, however, the characteristic occurrence of spontaneous remissions and are extremely cautious in drawing any conclusions. They have no hesitation in suggesting that the drug may be useful in milder forms of the disease and that it may help to bring about improvement in the underlying condition. Further studies with this particular therapeutic agent will be of extreme interest.

While discussing diseases of the large bowel it is proper to refer to a report by Mansans.[119] This concerns only a single pedunculated rectal tumor, but the conclusions drawn from the case are of direct clinical importance. The rectal tumor was removed by diathermy, and the procedure was followed by the development of peritonitis and death.

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117. Arnold, L.: The Bactericidal Action of Pectin and Metal Pectinates, Am. J. Digest. Dis. **6**:104, 1939.

118. Bannick, E. G.; Brown, A. E., and Foster, F. P.: Therapeutic Effectiveness and Toxicity of Sulfanilamide and Several Related Compounds: Further Clinical Observations, J. A. M. A. **111**:770 (Aug. 27) 1938.

119. Mansans, B. J.: Tumors with Hollow Peduncle, Nederl. tijdschr. v. geneesk. **82**:5297, 1938.

Microscopic examination of the tumor showed adenocarcinoma which had grown deep into the muscularis. The entire thickness of the muscularis, as well as the serosa, was found in the removed portion, indicating that the surgeon had unwittingly removed a part of the intestinal wall. The author cites 2 cases of gastric tumor in which the wall of the stomach was drawn up into the tumor so that the growth appeared to have a peduncle. He points out the danger of attempting removal of such a tumor inasmuch as section of the apparent peduncle results in a fairly large opening, as noted in the aforementioned case. An additional point of caution which he might have stressed is the real danger of removing a rectal growth by simple cauterization.

GENERAL CLINICAL CONSIDERATIONS

Of general interest is the discussion by Bishop [120] on the relationship between gastroenterology and cardiology. He presents a summary of the points of confusion between cardiac symptoms and those due to diseases of the gastrointestinal tract. These are considered under several headings: First, he considers symptoms due to mechanical disturbances affecting the abdominal viscera, such as emboli or aneurysms; he then mentions the effect of pathologic conditions in the abdomen on the cardiovascular system and refers, for example, to the effect of extreme flatulence on the activity of the heart of a susceptible person; he also emphasizes that overlapping areas of referred pain give diagnostic difficulty in differentiating between coronary disease, pericarditis and diseases of the gallbladder or stomach. He suggests that the presence of jaundice with its associated digestive disturbances may render the cardiovascular apparatus more easily subject to functional disturbances. Attention is called to the recognized important fact that patients having obvious coronary disease and gallstones are sometimes rendered free from cardiac symptoms after cholecystectomy. He also states, without detailed evidence, that in such cases the electrocardiogram may return to normal after cholecystectomy and further suggests that abnormal electrocardiographic changes in the presence of biliary tract disease may be due to associated vagal disturbances occurring with nausea and retching. The article contains nothing definitely new but brings up important clinical considerations that are worthy of repetition.

The ever increasing interest in the clinical and therapeutic implications of avitaminosis continues to be manifest. Among the numerous articles that have appeared on the protean manifestations of vitamin lack, several may be mentioned for their application to the problems of

120. Bishop, L. F., Jr.: Gastro-Enterology in the Practice of Cardiology, J. A. M. A. **112**:33 (Jan. 7) 1939.

gastroenterology. Among others, Musser and Sodeman [121] review the gastrointestinal expressions of avitaminosis. They maintain that subclinical expressions of scurvy, beriberi and rickets are common in the realm of alimentary tract disease. Under three headings they discuss the specific deficiencies, chronic dietary deficiency and conditioned deficiency.

Two authoritative articles by Cowgill [122] should be read by all who are interested in the treatment of patients apparently suffering from the lack of vitamin B_1. In these articles Cowgill discusses the requirements of the normal adult and child, mother and infant, and pays particular attention to the loss of vitamin B_1 through excretory channels. The last consideration is of extreme importance from the point of view of the widespread therapeutic use of thiamin chloride. There is an appreciable loss of this substance in the presence of pronounced diuresis and also as a result of diarrhea. In patients suffering from diarrhea the lack of this vitamin is frequently to be noted, and Cowgill's suggestion that adequate administration of vitamin B_1 under such circumstances can be obtained only by its parenteral use is timely and important.

Further observations on the value of nicotinic acid have appeared during the year. Of these, the most important are those of Spies and collaborators,[123] together with a similar article by Matthews.[124] All these observers agree as to the remarkable efficacy of nicotinc acid in the treatment of pellagrous glossitis, stomatitis, vaginitis, urethritis and proctitis.

Snell [125] discusses in an interesting fashion tropical and nontropical sprue on the basis of observations made on 46 patients. Of these, 14 acquired sprue in the tropics, and 32 had what was diagnosed as non-

121. Musser, J. H., and Sodeman, W. A.: Gastro-Intestinal Expressions of Avitaminosis, South. M. J. **31**:897, 1938.

122. Dann, M., and Cowgill, G. R.: Influence of Diarrhea on Vitamin B_1 Requirement, Arch. Int. Med. **62**:137 (July) 1938. Cowgill, G. R.: Human Requirements for Vitamin B_1, J. A. M. A. **111**:1009 (Sept. 10) 1938.

123. Spies, T. D.; Bean, W. B., and Stone, R. E.: The Treatment of Subclinical and Classic Pellagra: Use of Nicotinic Acid, Nicotinic Acid Amide and Sodium Nicotinate, with Special Reference to the Vasodilator Action and the Effect on Mental Symptoms, J. A. M. A. **111**:584 (Aug. 13) 1938. Spies, T. D.; Cooper, C., and Blankenhorn, M. A.: Use of Nicotinic Acid in the Treatment of Pellagra, ibid. **110**:622 (Feb. 26) 1938. Vilter, S. P.; Bean, W. B., and Spies, T. D.: Further Observations on Effect of 2,6-Dimethyl Dinicotinic Acid and Dinicotinic Acid on Pellagrins in Relapse and on Normal Persons, South. M. J. **31**:1163, 1938.

124. Matthews, R. S.: Pellagra and Nicotinic Acid, J. A. M. A. **111**:1148 (Sept. 24) 1938.

125. Snell, A. M.: Tropical and Non-Tropical Sprue (Chronic Idiopathic Steatorrhea): Their Probable Interrelationship, Ann. Int. Med. **12**:1632, 1939.

tropical sprue or idiopathic steatorrhea, acquired in central and north central states. In comparing the two groups Snell points out that so-called nontropical sprue differs from the tropical variety chiefly because of its extreme chronicity and the associated tendency toward disturbance of calcium metabolism and skeletal deformities. It is identical in all respects to the idiopathic steatorrhea cases of which have been reported in English and Scandinavian literature. The response to liver seemed best in those 20 patients whose condition most closely resembled tropical sprue, although in the remaining 12 occasional good results were obtained with adequate liver therapy. The report represents an excellent summary of an interesting and little known disease.

Brull and collaborators [126] also discuss nontropical sprue and report the results of a careful study of 4 cases of chronic diarrhea characterized by steatorrhea, a large deficit in intestinal absorption of calcium and phosphorus and resulting demineralization as evidenced by osteoporosis, hypocalcemia and tetany. The secondary clinical manifestations in these cases consisted of evidences of complex avitaminosis. The authors consider that the steatorrhea depends on B_2 (riboflavin) deficiency and think that the process of decalcification has the same fundamental origin. Melanoderma disappeared in these cases after treatment with lemon juice or solutions rich in water-soluble vitamins. Anemia was corrected by liver therapy, and disorders in phosphorus metabolism were treated by the administration of vitamin D. Any evidence of plasma vitamin A deficiency was treated by administration of this substance. The observations presented indicate that patients with this disease have a more or less deficient secretion of pepsin, hydrochloric acid, bile salts and lipase, but this is not particularly surprising in view of the known changes in the mucosa of the alimentary tract that take place in pronounced deficiency states. Brull points out that the entire symptomatic complex can be corrected by appropriate therapy but without counteracting the fundamental disorder, namely, a tendency to steatorrhea.

Of similar interest are several articles on the relationship between the alimentary tract and hemopoiesis. Brock,[127] in discussing intestinal strictures, gives a detailed description of 2 patients in whom megalocytic anemia occurred in association with intestinal strictures. The first patient had suffered for many years from a spruelike syndrome, and at autopsy showed multiple intestinal stenoses. The second patient's anemia apparently followed tuberculous enteritis and responded to

126. Brull, L.; Lambrechts, A., and Barac, G.: Sprue non tropicale: Etude approfondie de quatre cas observés en Belgique, Rev. belge sc. méd. **10**:457, 1938.

127. Brock, J. F.: Intestinal Stricture and Megalocytic Anaemia, Lancet **1**:72, 1939.

liver administered parenterally but not to liver given by mouth. It seems reasonable that in each patient the anemia developed because of lack of absorption of a hemopoietic factor by a damaged intestinal tract.

Sturgis and Goldhamer [128] also contribute observations on this subject. They present a rather interesting compilation of cases collected over eleven years and including various types of gastrointestinal lesions associated with macrocytic anemia. Of special interest are certain cases in which complete disappearance of the anemia followed relief of the intestinal condition, without the addition of any antianemic therapy. In another case macrocytic anemia improved with relief of chronic partial obstruction of the small bowel and recurred when this reappeared. These conditions do not represent true addisonian anemia inasmuch as achlorhydria was frequently absent, and paresthesias and glossitis were uncommon. The authors observe that following gastric resection it appears that from two to five years are needed for the development of macrocytic anemia. They suppose that several factors are operative and that the development of anemia depends on the degree of gastric or intestinal impairment of function and on the amount of reserve erythrocyte maturing material stored in the liver and elsewhere, as well as possibly on the age of the patient and the presence of infection. It is possible that this apparent delay in the development of macrocytic anemia after subtotal gastrectomy, as noted by Sturgis, may account for the absence of reports in the literature describing this condition. Quite possibly such reports are premature, and further accounts will appear in future years as the performance of subtotal gastrectomy becomes more common.

An article by Meulengracht [129] based on a histologic study of the pyloric gland organ in pernicious anemia is of interest because of its divergence from the present day conception of this disease. Meulengracht's investigations were based on postmortem histologic examination of the stomach and duodenum in 8 cases of pernicious anemia. He demonstrated pronounced changes in the fundus, with atrophy of the glands and disappearance of special gland elements. Much less definite changes were noted in the pylorus, where the pyloric glands seemed to be well preserved, and no changes were observed in Brunner's glands. These pathologic observations are similar to those made by Faber and Block in 1900 but are at distinct variation with the observations of Brown published in 1934 as a result of autopsy studies in 151 cases proved to be cases of pernicious anemia. Brown's observations seemed

128. Sturgis, C. C., and Goldhamer, S. M.: Macrocytic Anemia Other Than Pernicious Anemia Associated with Lesions of the Gastro-Intestinal Tract, Ann. Int. Med. **12**:1245, 1939.

129. Meulengracht, E.: Histologic Investigations on Pylorus Gland Organ in Pernicious Anemia, Nord. med. tidskr. **1**:11, 1939.

to coincide with the theory that changes in the mucosa of the pylorus and duodenum are the chief cause of pernicious anemia. The so-called pyloric organ, consisting of Brunner's glands of the antrum and duodenum, has been believed to secrete Castle's "intrinsic factor." It is obvious that the two sets of observations are not entirely compatible, and Meulengracht discusses the possibility of correlating his results with the present conception of the genesis of pernicious anemia. He suggests that the disease results from a failure of the interaction between the intrinsic and the extrinsic factor which originates a third principle, or liver factor, and that such a failure must be ascribed to disturbances of the small intestine. The discussion is largely of academic interest, but it must be admitted that Meulengracht's suggestion may have some bearing at least on the macrocytic anemias referred to in the preceding articles.

Recognition of the role played by the autonomic nervous system in the production of colonic symptoms is evidenced in the work reported by Leriche and collaborators[130] on the treatment of spastic colitis. The authors report their experience in the treatment of certain forms of spastic colitis by infiltration of the lumbar sympathetic and section of the splanchnic nerves. Nine patients were so treated. Usually the pain ceased after the first injection into the left lumbar sympathetic trunk, and after a second injection constipation was relieved to the extent that daily dejections were obtained without the use of laxatives. In a few cases of persistent right-sided pain it was necessary to infiltrate the lumbar sympathetic nerves on the right side. In a patient who was reexamined eighteen months after three infiltrations had been performed, although the symptoms had disappeared, roentgen evidence of spasticity in the colon persisted. The injections appeared to have modified the functional or neurogenic element without producing any anatomic changes in the intestine. No explanation is given of this apparent discrepancy. Another patient with intractable constipation noted the appearance of daily bowel movements without the use of laxatives seven days after an operation which consisted in resection of the left splanchnic nerve and first lumbar ganglion, and the improvement continued during the period of sixteen months' observation. The authors call attention to the need for careful study in such cases, inasmuch as not all patients can be benefited by such procedures. The findings reported by these investigators are of interest, inasmuch as measures tending to block parasympathetic activity are the usual ones employed to relieve so-called spastic colitis. Surgical revision of the sympathetic nerves has been used in the past only to permit more normal

130. Leriche, R.; Kunlin, J., and Froehlich, F.: Infiltrations novocaïniques du sympathique lombaire et section du splanchnique dans certaines colites spansmodiques, Progrès méd. **67**:11, 1939.

peristalsis by removing anything that inhibits parasympathetic activity. It is probable that the relief obtained in the cases described by Leriche and his collaborators was due to interruption of sensory impulses carried over sympathetic fibers, rather than to any interference with abnormal motor activity.

In this connection an article by Wakefield and C. W. Mayo[131] is of interest. These authors discuss the functional or sociologic disorders of the colon, a rather remarkable subject for joint discussion by a psychiatrist and a surgeon. They point out that the vast majority of colonic disorders are undoubtedly functional, although many of them are of sufficient severity to warrant surgical intervention. It is to this group that so well known a surgeon as Mayo and his associate call attention. The article is well worth reading, not for the presentation of new material, but for a rational and proper approach to the consideration of psychosomatic disorders.

Wilbur and Mills,[132] also of the Mayo Clinic, likewise discuss functional digestive disturbances in a group of 354 patients. The article is of particular interest as it points out some mistakes that have been made in the diagnosis of functional indigestion. Actually, accurate diagnoses were made in 85 per cent of the cases, due to the fact that care was taken in establishing them. The patients were reexamined at an average of seven years after their first admission to the clinic, and at the second examination 39 were found to have organic disease of the gastrointestinal tract. Nineteen of these had duodenal ulcers, which appeared to be the commonest source of error. Other diagnoses were gastric ulcer, gallbladder disease, cancer of the stomach and, in addition, extraalimentary tract disease (12 cases), such as pernicious anemia, heart disease, hyperthyroidism and others. The article is of value because it demonstrates the possibility of establishing a correct diagnosis of functional indigestion if sufficient care is used. It also demonstrates the necessity of following "functional" conditions that do not show adequate response to therapy.

Klingman[133] also has written a rather interesting report on the treatment of neurogenic megacolon by drugs. He attempts to differentiate acquired megacolon into two types: one which he calls rectosigmoidal achalasia and a second in which the parasympathetic motor function fails to act effectively above the rectosigmoid. In the first type the failure of the rectosigmoid to relax is thought to be due to over-

131. Wakefield, E. G., and Mayo, C. W.: Functional or Sociologic Disorders of the Colon, J. A. M. A. **111**:1627 (Oct. 29) 1938.

132. Wilbur, D. L., and Mills, J. H.: How Accurate Is the Diagnosis of Functional Indigestion? Ann. Int. Med. **12**:821, 1938.

133. Klingman, W. O.: Treatment of Neurogenic Megacolon with Drugs, J. Pediat. **13**:805, 1939.

activity of sympathetic inhibition, with resulting spasm, or failure of the parasympathetic nervous system properly to inhibit the rectosigmoidal apparatus. The author chooses syntropan as the most effective drug to paralyze the parasympathetic nerves. Barium sulfate enema studies seem to indicate that in rectosigmoidal achalasia there is marked delay in the emptying of the rectosigmoidal apparatus. Where there is deficient motor function (parasympathetic nerves) of the colon above the rectosigmoid, a barium sulfate enema demonstrates good emptying of the lower part of the colon but retention of barium sulfate in the upper part. When roentgen examination establishes that the rectosigmoidal apparatus is functional, Klingman tries prostigmine. If normal function cannot be demonstrated, he advocates the use of amphetamine sulfate (benzedrine) or syntropan, and if there is no response to either of these methods he advises lumbar ganglionectomy and presacral resection.

Redon [134] reports a case of definite clinical interest because of the unequivocal nature of the specific findings. The patient presented severe pain on the right side of the abdomen, with moderate elevation of temperature. An emergency diagnosis of appendicitis was made, which was subsequently rejected by the surgeon, who considered the possibility of acute intussusception. At exploration, the ileocecal region showed a sparkling edematous mass and no other abnormality. An immediate diagnosis of Quincke's edema was made, and histologic examination of the appendix, which was removed, showed no sign of an inflammatory process. The diagnosis should have been suspected before operation because of the history, which included frequent urticarial crises, especially after the ingestion of fish, and the added statement that he had eaten fish and mussels just prior to the attack. The chief interest in the report is that it furnishes clear evidence of visceral urticaria as an explanation for a certain type of obscure abdominal symptoms.

Because of the increasing awareness that amebic infestation of the intestinal tract is not uncommon in this country, the roentgenologic study of amebiasis by Gómez [135] is worthy of attention. The author describes his findings in 10 patients with chronic amebiasis with digestive symptoms but without diarrhea and in 25 patients with acute or chronic amebiasis with active diarrhea. In each instance a barium sulfate meal and barium sulfate enemas formed the basis of the roentgen studies. Delay in the passage of barium sulfate from the stomach was the rule, but the duodenum and ileum appeared almost uniformly nor-

134. Redon, H.: Crise d'œdéme de Quincke viscéral simulant une appendicite aiguë, J. de chir. **53**:360, 1939.

135. Esguerra Gómez, G.: La radiología de la amibiasis, Rev. Fac. de med., Bogotá **7**:45, 1938.

mal. The cecum and especially the transverse colon showed increased segmentation of varying degrees, and the caliber of the colon was distinctly diminished. There was uneven distribution of barium sulfate through the colon, some of the colon appearing apparently normal, with deformities being noted at irregular intervals. These deformities, however, characteristically remained the same in a given patient and presented the general aspect of lesions associated with ulcerative colitis.

Two articles relative to giardiasis are of interest. Véghelyi,[136] of Budapest, in an examination of 1,391 children between the ages of 2 and 17, found evidence of giardia (lamblia) infestation in 155. Complete examinations were performed in 144 of these children; 32 gave evidence of other diseases, 20 had a positive tuberculin test, and 92 showed no evidence of any other disease. The last group was compared with a group of healthy children of the same age in regard to the presence of symptoms referable to the digestive tract. Some of the children who showed evidences of giardia infestation had no symptoms or approximately none. In more than half of the children, however, gastrointestinal complaints, such as anorexia, headache, dizziness and abdominal pain were present. At times, intense acute pain was noted over the cecum, independent of meals and occurring in cramplike attacks. Mucus, pus and blood had been seen in the feces in one fourth of the infested group; two thirds had irregular bowel movements. Examination of the lungs, heart and kidneys revealed no abnormalities in the entire group. A more striking difference between the healthy and the infested children was that 79 of the latter were underweight. There were no hepatic disorders, and the author feels that the symptoms and evidences of undernutrition were fundamentally due to an impairment of the absorption of food from an irritated alimentary tract. In 29 of 32 children the symptoms disappeared completely after treatment with acetarsone. Such treatment was followed by definite improvement in the blood and gain in weight. Unfortunately, no mention is made of the complete and lasting disappearance of Giardia from the stools. The article is well prepared, however, and the comparison with a group of normal controls presents fairly convincing evidence that giardiasis may be responsible for symptoms referable to the alimentary tract.

De Muro[137] discusses the treatment of patients with giardiasis and reports some results obtained in 15 who were treated with atabrine, introduced for the treatment of this condition by Galli-Valerio in 1937.

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136. Véghelyi, P.: Giardiasis in Children, Am. J. Dis. Child. **56**:1231, (Dec.) 1938.

137. de Muro, P.: Atebrinbehandlung bei Giardiasis (Lambliasis), Deutsche med. Wchnschr. **65**:262, 1939.

Of the 15 patients, 8 showed chronic colitis and 2 proctitis, and 5 were said to have symptoms referable to the intestinal and biliary systems. The atabrine was administered in the same fashion as to patients with malaria, over a period of five days. Examination of the stools and duodenal contents in 13 cases gave negative findings for Lamblia after five days of treatment. The intramuscular administration of atabrine cleared the stools of Giardia but did not cause their disappearance from the duodenal contents. In each instance the disappearance of the parasites was followed with great improvement in symptoms and improvement in the character of the stools.

Reports have appeared from two groups of investigators on the value of phenolphthalein administered orally as a test of gastrointestinal ulceration, a procedure introduced by Woldman a year ago. Kremer, Shore and Wiesel [138] administered the drug orally to 137 patients and report the test correct for 56 per cent of them, showing gastrointestinal disease, with correct negative results for 79 per cent. Of 69 patients studied simultaneously by other routine procedures, the test was correct for 72 per cent. Patients with cardiovascular disease, infections, blood dyscrasias and certain other conditions without obvious disease of the digestive tract gave a number of falsely positive results. The authors conclude that the test may be valuable as an adjunct to other diagnostic methods, but that more must be learned of its use before it can be considered at all reliable.

Confirmation of this skeptical point of view is found in a report by Steigman and Dyniewicz.[139] These authors state that free phenolphthalein generally appears in the urine whenever the quantity of conjugated phenolphthalein in any one specimen exceeds 5 mg. per hundred cubic centimeters of urine. In some abnormal conditions, such as cardiac or renal disturbances and diseases of the blood, free phenolphthalein may appear at an even lower level. In a fair proportion of patients with nonulcerous diseases and of normal persons such a concentration is reached after ingestion of the test dose of phenolphthalein devised by Woldman; hence the appearance of free phenolphthalein in the urine cannot be considered as diagnostic evidence of ulceration in the intestinal tract.

Although any attempt to review the literature on infectious diseases involving the gastrointestinal tract is beyond the scope of this paper, it may be proper to mention the relatively frequent reports that have

138. Kremer, D. N.; Shore, P. D., and Wiesel, B. H.: Phenolphthalein as a Test in Gastro-Intestinal Disease, Am. J. Digest. Dis. **6**:192, 1939.

139. Steigman, L., and Dyniewicz, J. M.: Urinary Elimination of Free Phenolphthalein No Test for Gastro-Intestinal Ulceration, Am. J. Digest. Dis. **6**:120, 1939.

appeared on outbreaks of bacillary dysentery in other than subtropical areas. Bowes [140] gives an interesting account of Sonne dysentery due to milk, which involved 59 of 106 households in a given area in England. Blatt and Shaw [141] record a study of 356 children with bacillary dysentery from the children's division of the Cook County Hospital in Chicago. Another article by Lammerts van Bueren and de Haas,[142] although it comes from Batavia, is of some interest inasmuch as these writers report that among 400 children with bacillary dysentery observed at the Children's Clinic there were 160 nurslings, 11 of whom were less than 6 months old. The authors conclude that bacillary dysentery may attack children even during the first three months of life irrespective of whether they are bottle or breast fed; they comment on the fact that the feces of affected nurslings are usually less dysenteric in character than those of older children with this disease.

A possible contribution to the solution of the problem of local tissue immunity is found in an article by Torikata and Imaizumi [143] on local intestinal immunity. These authors administered daily oral doses of heat-killed colon bacilli to guinea pigs, with control immunization of other animals by routine subcutaneous methods. Ten days after the final administration of the vaccine, serums were withdrawn from each group of animals, and expressed tissue juices were prepared from the walls of the intestinal tract. Titrations of these serums and tissue juices showed an 80 to 100 per cent increase in opsonic titer of the intestinal tissues as a result of the oral administration of vaccine, but only a 10 to 20 per cent increase in the blood serum. In the control group there was a 76 to 100 per cent increase in the opsonic index of the blood stream, with less than half of that percentage in the intestinal tissue juices. The authors conclude that oral immunization with heat-killed Bacillus coli is effective in rendering the intestinal tract refractory to homologous infections long before effective humoral or somatic immunity is produced. An additional comment in this article quite properly points out the potential value of such studies, which should encourage further investigation relative to the route of administration of vaccines.

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140. Bowes, G. K.: Outbreak of Sonne Dysentery Due to Consumption of Milk, Brit. M. J. **1**:1092, 1938.

141. Blatt, M. L., and Shaw, N. G.: Bacillary Dysentery in Children: Study of Three Hundred and Fifty-Six Cases from the Children's Division in the Cook County Hospital, Chicago, Arch. Path. **26**:216 (July) 1938.

142. Lammerts van Bueren, B., and de Haas, J. H.: Bacillary Dysentery in Young Nurslings, Maandschr. v. kindergeneesk. **7**:461, 1938.

143. Torikata, R., and Imaizumi, M.: Zum Unterschiede zwischen der Injektions- und der oralen Immunisierung, Ztschr. f. Immunitätsforsch. u. exper. Therap. **94**:342, 1938.

In the field of preventive medicine, two recent articles seem to be of extreme importance. Trask and his associates [144] made a very careful study of a small epidemic of poliomyelitis. Since the original observations in 1912 by Kling and his collaborators, few investigators have successfully isolated the virus of this disease from the human intestinal tract, although one brief mention was made by Harmon of a successful attempt in 1937. Trask and associates isolated the virus from the stools three times in a single case. The child whose stools contained the virus was ill for only three or four days, but the virus persisted in the stools for at least twenty-four days from the onset of this mild illness. Although the authors do not imply that the virus necessarily enters the body by way of the gastrointestinal tract, they point out the seasonal prevalence of poliomyelitis, which, like typhoid and dysentery, occurs largely in the summer. They also mention a fact that is not so well known, namely, the presence of lesions in the intestinal tract. The writers suggest that during an epidemic of poliomyelitis the common mild and often unrecognized forms of the disease may be responsible for a high degree of pollution of the sewage with poliomyelitis virus. Kramer, Hoskwith and Grossman [145] report the isolation of the virus from the upper intestinal segment of a monkey killed at the height of the disease. The virus apparently is able to withstand acidity, and this finding emphasizes the extreme importance of a proper disposal of feces from patients suffering from poliomyelitis, particularly in small communities with inadequate sewage disposal facilities.

144. Trask, J. D.; Vignec, A. J., and Paul, J. R.: Poliomyelitis Virus in Human Stools, J. A. M. A. **111**:6 (July 2) 1938.

145. Kramer, S. D.; Hoskwith, B., and Grossman, L. H.: Detection of the Virus of Poliomyelitis in the Nose and Throat and Gastro-Intestinal Tract of Human Beings and Monkeys, J. Exper. Med. **69**:49, 1939.

Book Reviews

The Endocrine Glands. By Max A. Goldzieher, M.D., Endocrinologist, Gouverneur Hospital and Brooklyn Women's Hospital. Price, $10. Pp. 916, with 271 illustrations. New York: D. Appleton-Century Company, Inc., 1939.

As stated in the preface, the aim of the author was to provide a "book which discusses with equal thoroughness and on the basis of first hand information both the theoretical and practical aspects of endocrinology." The first section is concerned with general principles of endocrinology and the relation to other fields. Succeeding sections deal in turn with the individual endocrine glands, including the thymus and the pineal body. Each of these sections includes brief chapters on historical material and on the embryology, anatomy, histology and physiology of the gland in question. These are followed by a chapter on morbid anatomy. Longer chapters discuss the various clinical disorders, their classification, etiology, pathogenesis, diagnosis and therapy. References to the literature, conveniently placed at the end of chapters or subjects, are liberally supplied. A large number of photographs of patients and of histologic sections are provided.

The author shows a commendable reluctance to attribute endocrine functions to the thymus gland. A creditable case is made in support of the recent view that Cushing's syndrome is related more to adrenal than to pituitary hyperfunction. Various forms of adrenal insufficiency receive considerable attention. However, in many instances the cautious reader will reserve his opinion regarding the efficacy claimed or implied for some of the forms of endocrine therapy.

A commendable attempt is made throughout this book to correlate clinical and physiologic knowledge. The well informed reader will criticize or desire to qualify numerous statements, interpretations and implications made by the author. This is true of any book dealing with a subject concerning which more is to be learned than is known. The book will serve as a good text if the limitation of existing knowledge is kept in mind and if some of the opinions and the therapeutic suggestions of the author are not taken too literally and considered as established.

Cause and Prevention of Disease. By William Harvey Perkins, Professor of Preventive Medicine, Tulane University of Louisiana. Price, $7.50. Pp. 713, with 1 diagram and many tables. Philadelphia: Lea and Febiger, 1938.

The author has gathered in a single volume a great many facts which bear on the cause and prevention of disease.

Various direct or indirect causes are discussed under six headings. Heredity, nutrition, chemical agents, physical agents, animate agents and psychobiologic or biosocial factors are each given credit, either alone or in combination, for causing illness. The author's method of approach to discussing the cause of disease is to arrange these different agents in various classes according to their characteristics and to their effect.

The preventive measures that may be employed against these agents are considered collectively and individually. There is a tendency toward repetition, but, on the whole, the work is an excellent reference book for physicians and students who wish to obtain a quick résumé of a particular subject in the field of preventive medicine.

From the standpoint of a textbook for medical schools, the book does not fully meet the practical needs of the student. It does not cover completely the practical application of technical methods in the field of public health. In certain parts of the text the style and phraseology are involved, making rapid assimilation difficult. The proportionate allotment of space for any subject does not always

coincide with its relative importance; for instance, a disproportionate amount of space, one quarter of the book, is devoted to a detailed account of the exogenous chemical agents and their toxicology. However, the author is to be congratulated on his compilation of a condensed but inclusive review of so difficult a subject as the causes of disease and the methods of prevention.

On the Stability of Transfused Erythrocytes. By H. J. N. Dekkers. Pp. 104. Amsterdam: Scheltema & Holkema, 1938.

The estimations of the duration of life of the erythrocyte vary—with the author and the method of approach employed—from fifteen to two hundred days. Heretofore, practically all methods had to be limited to indirect procedures. The finding of the existence of blood groups M and N (Landsteiner and Levine, 1927) made possible the direct identification of transfused compatible red blood cells. The author found the average time for existence of erythrocytes after transfusion of 500 cc. of blood to the seventy-five and one-half days by microscopic evidence of heteroagglutination and fifty-four and one-half days by macroscopic evidence. The results of more than one hundred transfusions could be traced until after the disappearance of all the cells of the donor in 12 cases only. Four additional patients were traced forty-two to seventy-six days after the transfusion, at which time transfused erythrocytes were still present. Eight patients with secondary types of anemia, in whom disease leading to increased destruction of erythrocytes can be supposed to have been absent, showed the presence of transfused cells after fifty-nine to ninety-five days. The maximal erythrocytic survival in 1 case of toxemia of pregnancy, with uremia and solution of the placenta, was forty-five days, in 1 case of staphylococcic sepsis it was forty days, in 1 case of subacute myeloid leukemia it was twenty-three days and in 1 case of pernicious anemia it was seventy-six days (thus being within normal limits).

Internal Medicine: Its Theory and Practice in Contributions by American Authors. Edited by John H. Musser, B.S., M.D., F.A.C.P.; Professor of Medicine in the Tulane University of Louisana School of Medicine; Senior Visiting Physician to the Charity Hospital, New Orleans. Third Edition. Price, $10. Pp. 1428, with 18 tables and 37 illustrations. Philadelphia: Lea and Febiger, 1938.

The first edition of this textbook appeared in 1932. The ARCHIVES liked it, complimented it and at the same time proved a good fortune-teller. The ARCHIVES said: "On the whole, the new textbook is admirable. Teachers, students and practitioners will enjoy it, not only because it is well and clearly written, but also because it opens up the vast field of medical knowledge in a simple, interesting and engaging manner."

That teachers, students and practitioners have enjoyed the book is obvious, for only a popular, widely read text could make necessary three editions in six years.

Osler's "Practice of Medicine" accomplished the same feat. The first edition of Osler's text appeared in 1892, the third in 1898. In those days, apparently, medical knowledge developed at about the same pace as nowadays; the third edition of Osler's book was 131 pages longer than the first; the third edition of Musser's book is 112 pages longer than the first.

In the preface to the latest edition Musser states that his "Internal Medicine" has undergone careful scrutiny and extensive revision since its birth. New knowledge and ideas have been incorporated in the 1938 model; new concepts of pathologic physiology are described, and new forms of therapy are discussed. On the whole, once again the ARCHIVES compliments the book. It is up-to-date. It continues to open up the vast field of medical knowledge in a sensible, interesting and engaging manner. It is certain to be popular.

Progressive Relaxation. By Edmund Jacobson, A.M., Ph.D., M.D. Second Edition. Price, $5. Pp. 493, with illustrations. Chicago: The University of Chicago Press, 1938.

The value of rest as a therapeutic measure has long been appreciated, but the study of relaxation from a scientific standpoint is a comparatively new venture ably undertaken by the author of this book.

The importance of "neuromuscular hypertension" in many organic and functional states is discussed, and the efficacy of relaxation in the treatment of these conditions is indicated. The technic of progressive relaxation which is used by the author is described clearly and in detail. An interesting series of experiments is reported in which the effect of relaxation on the knee jerk is recorded graphically. A study of the relation of mental processes and of emotions to muscular tension is presented, together with a method of measuring neuromuscular processes in mental activities. Apparatus and procedures are described which may be used to measure in electrical terms all degrees of muscular contraction. These procedures may be of clinical use in the accurate determination of tension in patients who exhibit this symptom. A complete bibliography is included at the end of the book.

This work is an original and noteworthy contribution to a new field of investigation which should be of interest to the neuropsychiatrist, the physiologist, the internist and all others who deal with problems of the tense patient.

Survey of Carbon Disulphide and Hydrogen Sulphide Hazards in the Viscose Rayon Industry. Bulletin 46, Division of Occupational Disease Prevention, Commonwealth of Pennsylvania, Department of Labor and Industry, 1938.

This bulletin of 69 pages deals with a specific industrial poison in the rayon industry. Each aspect of this occupational disease problem is discussed in detail by a writer especially qualified by training and experience. The authors include members of the Pennsylvania Department of Labor and Industry, the United States Department of Labor and the faculties of the University of Pennsylvania and the Pennsylvania State College.

The pamphlet is well written and well arranged. Its publication is timely and will be welcomed by all those interested in the field of industrial health. One regrets the apparent political necessity of the frequent repetition of names of politicians in the first eight pages.

A Historical Chronology of Tuberculosis. By Richard M. Burke. Price, $1.50. Pp. 81, with 1 chart. Springfield, Ill., and Baltimore: Charles C. Thomas, Publisher, 1938.

From the beginning of history to 1938, the author outlines by brief statements the development of knowledge of tuberculosis. Under the year 1885, for example, among several items, one reads that "Edward Livingston Trudeau (1847-1915) founds Adirondack Cottage Sanatorium at Saranac Lake, New York. Employs bed rest in the presence of symptoms. He becomes patron saint of the American consumptive." In sixty-three pages of this sort of treatment a vast amount of ground is covered, and every physician should find this compendium indispensable. Finally, there are indexes of names and subjects and a large chart showing in tabular form the most important matters dealt with in the text.

Les dystrophies dentaires de la syphilis héréditaire. By Lucien Lebourg. Price, 38 francs. Pp. 164. Paris: Gaston Doin & Cie, 1939.

This is an excellent monograph on the changes that take place in the teeth of the child or adult who has inherited syphilis. The book is of considerable cultural interest to the physician and undoubtedly will be of great practical interest to the dentist.

News and Comment

New York Diabetes Association, Inc.—The New York Diabetes Association, Inc., offers three grants of up to $500 each for research in diabetes. These grants may be used for the purchase of apparatus and supplies that are needed for special investigations, and for the payment of unusual expenses incident to such investigations, including technical assistance, but not for providing apparatus and materials which are ordinarily a part of laboratory equipment. The researches must be carried out in Greater New York, although the persons engaged in them need not be residents of Greater New York.

Letters asking for aid must state definitely the qualifications of the investigator, an accurate description of the proposed research, the size of the grant requested and the specific use of the money to be expended. It is highly desirable to include a list of men with whom the applicant has been and is associated who would be willing to give letters of recommendation and sponsor the applicant. Applications should be mailed to the Committee on Research, New York Diabetes Association, Inc., 22 East Fortieth Street, New York.

Applications will be received up to Nov. 1, 1939.

Seventh International Congress on Rheumatism.—The subjects to be discussed at the Seventh International Congress on Rheumatism, to be held in New York, Philadelphia and Boston, June 1 to 10, 1940, will be: infection, nutrition and treatment. Free lectures will be given afterward.

Besides a visit to the World's Fair, which it is expected will still be open, the American Medical Association has organized a scientific exhibit in the field of medicine, which will in itself undoubtedly be worth a visit to the United States.

Further information regarding this congress may be procured from the International Bureau, Keizersgracht 489, Amsterdam, Netherlands.

Obituaries

WILLIAM J. MAYO, M.D.
1861-1939

Dr. William J. Mayo was one of the great medical figures of these times. Every one knew his name. His influence on present day medicine as well as surgery is perceptible in many ways.

Dr. Mayo was a great clinical teacher. He was lukewarm to undergraduate teaching, feeling that what could be taught of medicine to undergraduates was, on the whole, elementary and that in the making of the finished product, particularly in surgery, systematized post-graduate training was essential.

His method of teaching was entirely personal. He had little confidence in pedagogic formalities. He believed that the most effective way to teach was by the method of learning. He himself always was eager to learn, and so it was that he worked every day in the clinic, seeing patients, rubbing elbows with his students and, by force of example, setting them a pace to do better work and thereby get a better education.

He felt that experience was the greatest teacher of all. This was true in his case: He was familiar with every phase of disease.

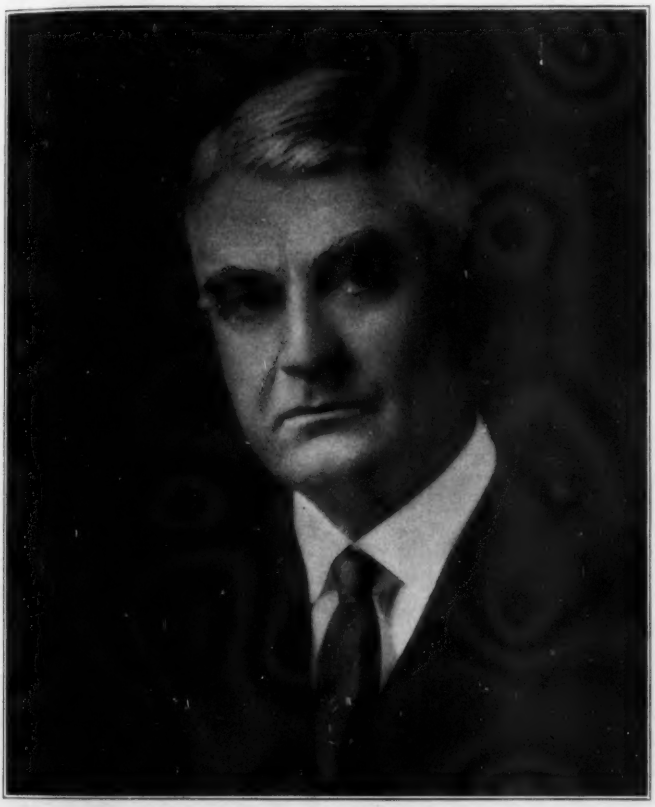
Dr. Mayo believed in imaginative persons. That was one of the reasons why he liked to be surrounded by young men. He felt that as one grew older one tended to become conservative, gaining, perhaps, in judgment but, on the other hand, losing in ability to look ahead. He dreaded anything static.

One day on the Mississippi River he remarked, as he watched the current flow past, that American medicine is much like a river. Some of today's medical schools with their elaborate equipment are like bits of wood caught in an eddy. They go round and round, stirring up a certain amount of foam but making no headway. On the other hand, other schools less cumbersome are being so adroitly piloted as to avoid the eddies and are going downstream serenely. He feared medical complacency. He wished to see medical knowledge advance steadily.

He believed in the American Medical Association. He said that all physicians belonged to a common brotherhood. Some, by the grace of God, were more fortunate than others, and those who could should work for the benefit of the rest. He felt that the way to be of greatest

service to all is through loyalty to the Association. Of his various honors he prized the Presidency of the American Medical Association among the highest.

He was no showman. He believed, however, that one should learn how to talk without notes or hesitation, briefly and clearly, and should



WILLIAM J. MAYO, M.D.
1861-1939

know how to assemble material in readable form, well illustrated and well expressed. The result of this discipline has been obvious. A medical paper from the Mayo Clinic almost invariably is well done. A speaker from the clinic almost invariably is interesting and instructive.

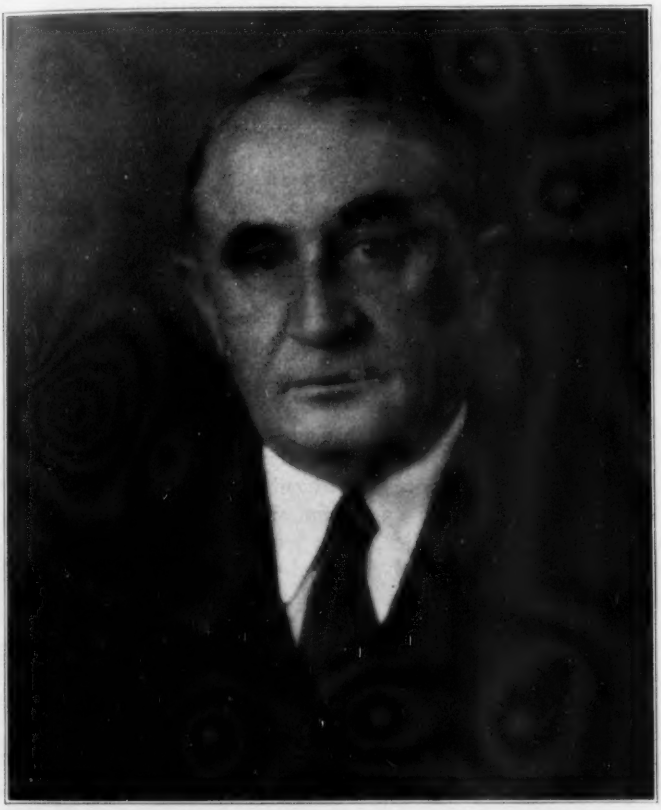
Dr. Mayo was not particularly concerned over the bugbear of socialized medicine. He took pride in being an American citizen and had unbounded confidence in the country's future. He thought that the ordinary person wished to pay for medical service and would do so gladly if the cost could be kept within reasonable limits. He strove to offer to his patients the highest type of service at moderate cost. This became the fundamental policy of the clinic.

Dr. Mayo believed that the Mayo Clinic belonged to the patients. It seemed to him that the wisest way through which to safeguard their future health was by investing in postgraduate medical education the money which they had placed in his hands. With this concept the Mayo Foundation was first established and since has grown into a great postgraduate medical school.

Persons from all parts of the world have been trained in the Mayo Clinic. In nearly every medical center some one from the Mayo Clinic is at work, trying as bravely as he can to carry forward Dr. Mayo's precepts. This fact, as well as any other, epitomizes Dr. Mayo's work. He was proud of even the humblest accomplishments of any of those who had worked under him. He was a model teacher, not self seeking but content to let his pupils harvest the fruits of his planting.

CHARLES H. MAYO, M.D.
1865-1939

Dr. Charles Horace Mayo died in a Chicago hospital in May 1939, known and mourned perhaps even more widely than his equally distinguished brother. He was a human person, Dr. Charlie, and had



CHARLES H. MAYO, M.D.
1865-1939

the gift of making lasting friends. He had the gift and made the effort. The world's most famous surgeon, in the golden age of surgery, was never too fatigued to include friendliness in his self-imposed prescription for medical care.

In the early annals of Rochester Dr. Charlie was the man who tried everything first. He operated on the first goiter among the Mayo

patients. He experimented with mica plates and the first x-ray apparatus. In the original building at St. Mary's Hospital an elevator is still in use which he planned and installed. He was forever on the watch for some new door to open. And each time he opened a door it was with some specific patient in mind.

He was a homely man in the classic sense. His accumulation of academic robes from institutions of learning the world over attests his high position in the professional world; he served as president to almost every medical and surgical society of which he was a member. And yet he served as health officer to the little city of Rochester at about the same time that he was President of the American Medical Association, and there is the perfectly authenticated story of his polishing the boots of a British guest. Dr. Mayo knew, as the guest did not, that household servants in America do not polish vagrant shoes left outside of bedroom doors. Visitors present at the University of Edinburgh when that institution honored him with their most distinguished degree reported that the traditionally solemn audience shouted with laughter at his acceptance speech. They were listening to words of dry humor, spoken in the accent of the American Middle West, and they sensed it to be the humor of another Mark Twain or a Will Rogers.

Had his been a less dynamic personality he might have spent his life playing second fiddle to his brilliant elder brother, but fortunately they complemented rather than obscured each other. It was Dr. Charlie's privilege to use his gifted hands to alleviate human suffering and his inventive mind to experiment with new methods of surgery. But it was a happy coincidence that one born with such gifts should also have been endowed with such unusual human understanding and sympathy to help when fingers and invention failed.